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Life Systems, Inc., Cleveland, OH

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on vinyl chloride. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of vinyl chloride
- Toxicokinetics and human exposure to vinyl chloride
- Health Effects of vinyl chloride in humans and animals
- Mechanisms of toxicity of vinyl chloride
- Quantification of toxicological effects of vinyl chloride

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I. SUMMARY

Almost seven billion pounds of vinyl chloride are produced in the United States annually. Most emissions into the environment originate from manufacturing plants which use the compound for the production of polyvinyl chloride resins. The predominant route of exposure to the public living near these plants is through inhalation, while the principal source of vinyl chloride exposure for most Americans is probably from polyvinyl chloride food containers. This source contributes approximately 1 ppb vinyl chloride to the diet. Vinyl chloride has also been found in drinking water. Three national surveys have demonstrated the presence of vinyl chloride at very low levels (μg/L range) in a small number of drinking water supplies.

Upon ingestion, vinyl chloride is rapidly absorbed from the gastrointestinal tract and is distributed to the liver and other organs. Several pathways may be involved in vinyl chloride metabolism, which occurs primarily in the liver. The toxicity of vinyl chloride appears to be attributable to its enzymatic conversion to reactive polar metabolites such as chloroacetaldehyde or chloroethylene oxide. Several of these suspected metabolites are mutagenic, but vinyl chloride itself is not mutagenic, according to available information. At low doses (e.g., 1 mg/kg) of vinyl chloride the metabolites are excreted primarily in the urine. At high doses (e.g., 100 mg/kg), most of the solvent is expired as vinyl chloride.

Acute and chronic exposure to vinyl chloride can result in toxicity in experimental animals and humans. In animals, an inhalation exposure of approximately 100,000 ppm results in death within several hours, with autopsies revealing congestion and edema of the lungs and hyperemia of the kidneys and liver. Test animals exposed to an air concentration below 100 ppm exhibit no pronounced adverse health effects. Vinyl chloride does not appear to be teratogenic in rats or rabbits, but insufficient data exist to evaluate the teratogenicity of vinyl chloride in humans.

Studies on humans working in vinyl chloride plants suggest that systemic toxic effects that are noncarcinogenic in nature can be demonstrated at exposure levels below 50 ppm. Some plant workers may have been exposed to concentrations exceeding 1,000 ppm and occasionally approaching 10,000 ppm before OSHA standards were instituted in 1974. At these levels, workers manifested dizziness, headaches and/or euphoria. Long-term exposure to these levels in vinyl chloride plants have resulted in numerous toxic effects (i.e., acroosteolysis, pulmonary insufficiency, cardiovascular and gastrointestinal manifestations and disturbances of the central nervous system). Unfortunately, data on dose-response relationships in humans are very scarce because there were few air measurements of vinyl chloride in the work environment before 1974.

Vinyl chloride is a proven carcinogen in mice, hamsters and rats. Animals studies have shown that vinyl chloride produces tumors of different types at different sites, and that the incidence and relative distribution of these tumors are influenced by dose, age of the animal and species and strain of animal used. Angiosarcomas of the liver were found in all animals studied, whereas some types of tumors, such as brain tumors, hepatomas and lung tumors, were observed in onlyone species of animal. A dose-response relationship was observed in most experiments. Inhalation studies have shown that 50 ppm is the lowest vinyl chloride exposure which has a carcinogenic effect. A recently completed ingestion study demonstrated the occurrence of hepatic angiosarcomas and pulmonary angiosarcomas in rats at levels of 5.0 mg/kg bw/day or more, and the increased incidence of foci of cellular alteration and liver cell tumors at the lowest exposure level of 1.7 mg/kg bw/day.

Human data have been obtained primarily from workers exposed to vinyl chloride. A number of epidemiologic studies have linked vinyl chloride with angiosarcoma and other forms of neoplasm. The reported frequency of angiosarcoma of the liver is especially noteworthy because this is a very rare type of cancer (25 to 30 cases/year in the United States), and it is, therefore, reasonable to infer a causal relationship between exposure to vinyl chloride and the development of this tumor. Through 1977, a total of 64 cases of liver angiosarcoma have been identified worldwide among vinyl chloride-exposed industrial workers. Although rare, the carcinogenicity of vinyl chloride to humans is unambiguous.

There is insufficient data available for calculation of one-day health advisories but the ten-day health advisories can be used as conservative estimates of one-day health advisories. Ten-day health advisories of 9.0 mg/L for an adult and 2.6 mg/L for a child were developed using the subchronic toxicity data in the study by Feron et al. (1975). An adjusted ADI of 0.046 mg/L for chronic noncarcinogenic effects was calculated using the liver lesion data in the lifetime carcinogenicity study in rats by Til et al. (1983).

The International Agency for Research on Cancer (IARC) analyzed the available data and concluded that exposure to vinyl chloride results in an increased carcinogenic risk to humans. The organs most likely to be affected are the liver, brain, lung and hemato- and lymphopoietic systems. The National Academy of Sciences (NAS) (1983) also examined the data an concluded that vinyl chloride is an established carcinogen in humans and animals, with older animals and females appearing to be more susceptible.

The NAS and EPA's Carcinogenic Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water by mathematical extrapolation from high-dose animal studies. Using the risk estimates generated by the NAS (1977 to 1979), in which the linear non-threshold multi-stage model was utilized, the range of vinyl chloride concentrations were computed that would nominally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption at the stated exposure level. From the NAS model it is estimated, at the 95% confidence limit, that consuming two liters per day with a vinyl chloride concentration of 100 µg/L, 10 µg/L or 1 µg/L would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed over a lifetime, respectively. Using the revised CAG approach and the multistage model, it was estimated, at the 95% confidence limit, that consuming two liters of water per day with a vinyl chloride concentration of 200 µg/L, 20 μg/L or 2 μg/L would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, over a lifetime respectively. The numerical differences between the NAS and CAG risk estimates are due to the selection of data for use in the model. The NAS based its calculations on an ingestion study by Maltoni et al. (1975) in which rats were exposed to vinyl chloride by gavage, while the CAG used the same Maltoni et al. (1975) study, but based its estimate upon the increased incidence of total tumors in rats exposed to vinyl chloride through inhalation.

The CAG has recalculated the cancer risk with the method described above and the Feron et al. (1981) data to estimate an increased risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed over a lifetime to a vinyl chloride concentration of 1.5, 0.15 or 0.015 μg/L, respectively. The CAG calculation based on the Feron et al. (1981) data is under reassessment to take into account new data by Til et al. (1983).

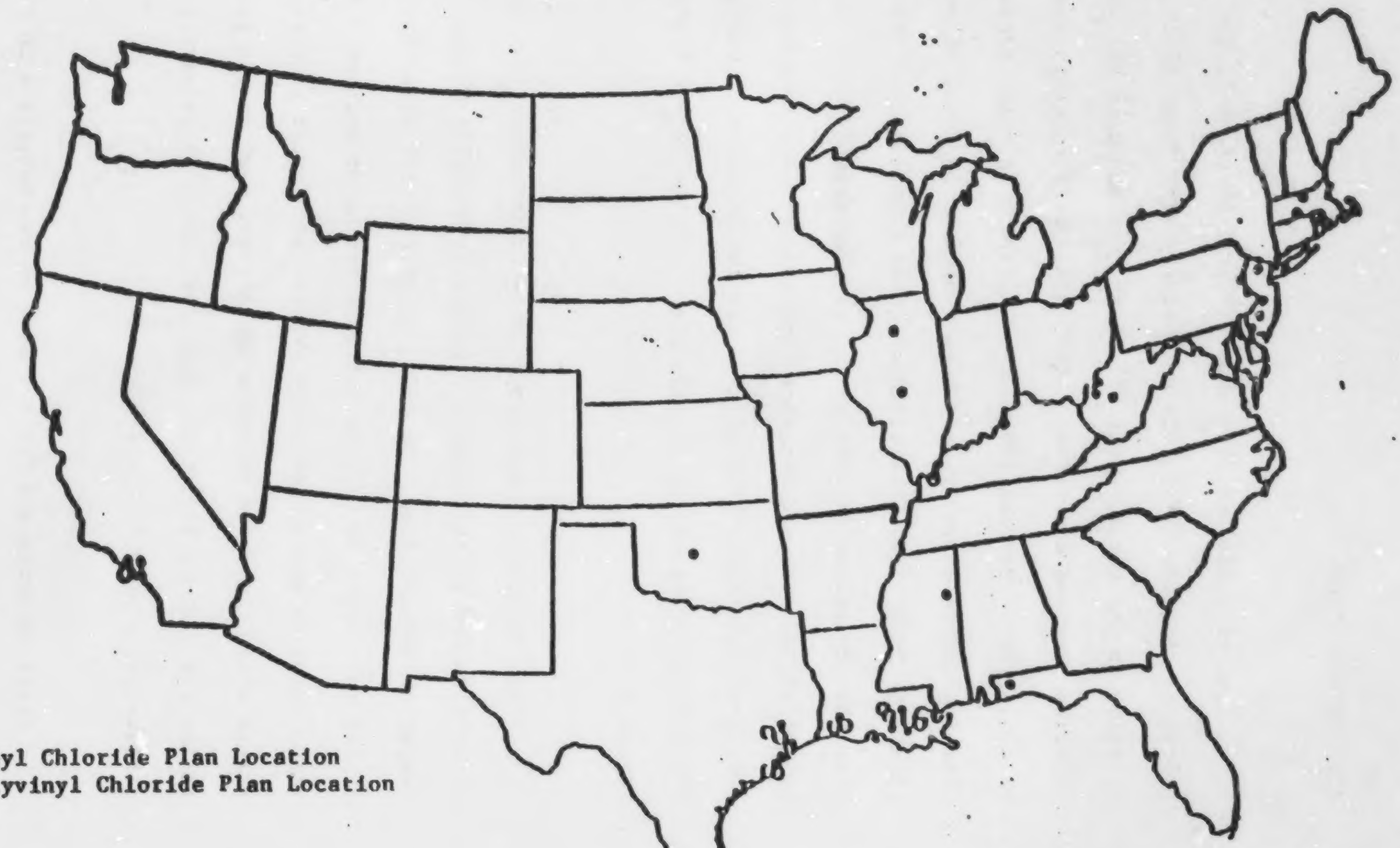
II. INTRODUCTION

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride (PVC), the most widely used material in the manufacture of plastics in the world. About 25% of the estimated 18 billion pounds of vinyl chloride produced worldwide in 1972 was manufactured in the United State (Berk et al., 1976). Between 1968 and 1973, vinyl chloride production in the United States rose 14% annually, reaching a production level of nearly seven billion pounds in 1978 (U.S. International Trade Commission). This increase in vinyl chloride production was due to the growing dependence of virtually every branch of industry and commerce upon products and components fabricated from polyvinyl chloride (USEPA 1974). For the location of vinyl chloride and PVC manufacturing and processing plants in the United States in 1978, refer to Figure II-1.

Vinyl chloride is not known to occur in nature (NAS 1977). The compound is synthesized as chlorinated olefinic hydrocarbon monomer from petrochemical feedstock and chlorine. In 1975, vinyl chloride emissions in the United States were found to originate from three major sources: (1) 17 plants where vinyl chloride was commercially synthesized (about 11 percent); (2) 41 PVC plants where the vinyl chloride monomer was used in the production of PVC resins for various industrial purposes (about 85 percent); (3) about 8,000 PVC fabricating plants (USEPA 1975b).

Vinyl chloride and PVC are used as raw materials in the rubber, paper, glass and automotive industries. In addition, vinyl chloride and PVC are used

Figure II-1 Locations of Vinyl Chloride and Polyvinyl Chloride Plants in the United States



○Vinyl Chloride Plan Location
●Polyvinyl Chloride Plan Location

○Puerto Rico

Source: SRI

Adapted from Milby, 1978.

in the manufacture of electrical wire insulation and cables, piping, industrial and household equipment, medical supplied, food packaging materials and building and construction products. PVC and vinyl chloride copolymers are distributed and processed in a variety of forms, including dry resins, plastisol (dispersions in plasticizers), organosol (dispersions in plasticizers plus volatile solvent), and latex (a colloidal dispersion in water used to coat paper, fabric or leather).

III. PHYSICAL AND CHEMICAL PROPERTIES

The structure of vinyl chloride is:

$H_2C = CHCl$ Molecular Weight = 62.5

Vinyl chloride is highly flammable (limits of inflammability: 4.00% to 21.70%) and in sufficient concentrations (at least 1,200 to 2,000 ppm) has a sweet, pleasant odor. The compound has a boiling point of -13.3°C. Thus, at standard temperature and pressure, vinyl chloride is a gas. Vinyl chloride is only sparingly soluble in water (0.11 g/100 g water at 28°C), but is soluble in alcohol and very soluble in ether and carbon tetrachloride. The specific gravity of the chemical is 0.91. The vapor density of vinyl chloride is slightly more than twice that of air (CRC Handbook of Chemistry and Physics 1978 to 1979, Braker and Mossman 1971).

The above information indicates that vinyl chloride is volatile and readily passes from water into the gas phase under most laboratory and environmental conditions. This was confirmed in experiments where 16 mg/L vinyl chloride was added to distilled water in beakers and the concentration determined with time (USEPA 1974). The data indicate that if first order kinetics are assumed, the volatilization half-life in quiescent water (unstirred) is 290 minutes, and in continually stirred water it is 25.8 minutes. Dilling et al. (1975) found similar values for volatilization from stirred water. As Dilling et al., noted, predictions of vinyl chloride loss from water at relatively high concentrations (e.g., 1 mg/L) may not reflect the situation at very low concentrations.

Volatilization appears to be the most significant process in the loss of vinyl chloride from the aquatic environment (Hill et al. 1976). Once in the atmosphere, vinyl chloride undergoes rapid photochemical oxidation (Gay et al. 1976), Lillian et al. 1975).

IV. PHARMACOKINETICS

A. Absorption and Distribution

An investigation by Duprat et al. (1977) indicated that inhaled vinyl chloride is rapidly absorbed by the lungs and immediately accumulates in the liver. In this study, rats were exposed in a chamber to 20,000 ppm ^{14}C vinyl chloride for five minutes, and then the distribution of radioactive vinyl chloride in the various body organs was determined. At ten minutes following treatment, radioactivity was found in the liver, bile duct, digestive lumen and kidneys. With increasing time (up to three hours), ^{14}C activity was detected in the urinary system, salivary and lacrimal glands, skin and thymus.

Using male Wistar rats, Withey (1976) determined that vinyl chloride is rapidly absorbed from the gastrointestinal tract following gastric intubation of aqueous solutions containing up to 2.0 mg/mL vinyl chloride. Vinyl chloride uptake by this route was extremely rapid; peak concentrations were found less than ten minutes after the dose was administered.

In a study by Watanabe et al. (1976a), rats were given single oral doses (gavage) of 0.05, 1 or 100 mg/kg of ^{14}C-vinyl chloride dissolved in corn oil, and the routes and rates of elimination of ^{14}C activity were followed for 72 hours. The percentage of the dose expired as vinyl chloride was 1%, 2% and 67%, respectively. The disposition of vinyl chloride to various organs and tissues was also determined. The liver was found to retain the greatest percentage of activity at all dose levels, three to five times the percentage found in muscle, lung or fat (Table IV-1). The investigators concluded that the fate of vinyl chloride following oral administration is a dose-dependent saturable process, with the saturation of the vinyl chloride-metabolizing enzymes occurring at a concentration between 1 and 100 mg/kg.

In an inhalation study by this group (Watanabe et al. 1976b), rats were exposed to 10 or 1,000 ppm ^{14}C-vinyl chloride for six hours and the routes and rates of elimination of ^{14}C activity were followed for 72 hours after termination of exposure. The animals were sacrificed after 72 hours and samples of tissues collected for analysis of ^{14}C activity. Table IV-2 indicates that, as in the gavage study, the liver retained the greatest percentage of vinyl chloride (or metabolites) at the dose levels studied. In contrast to the gavage experiment, however, no saturation of vinyl chloride metabolism was discernable between 10 ppm and 1,000 ppm in this study.

Bolt et al. (1976) also studied the tissue disposition of ^{14}C-vinyl chloride in rats. Immediately after exposure by inhalation of 50 ppm vinyl chloride for five hours in a closed system, the percentage of incorporated ^{14}C-radioactivity per g tissue was highest for kidney (2.13) and liver (1.86). The percent of incorporated activity was 0.73 for the spleen and 0.17 for the brain. Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

The percentage absorption of vinyl chloride from the human gastrointestinal tract has not been established. Because of the lack of data

Table IV-1 Percentage of the Administered ^{14}C Activity per Gram of Tissue After Administration of (^{14}C) Vinyl Chloride by Gavage to Male Sprague-Dawley Rats[a]

Tissue	Dose (mg/kg)[b]		
	0.05	1.0	100
Liver	0.172±0.025[c]	0.182±0.005	0.029±0.002
Skin	0.070±0.023	0.076±0.010	0.010±0.002
Carcass	0.027±0.007	0.046±0.002	0.007±0.001
Plasma	0.041±0.004	0.053±0.007	ND[d]
Muscle	0.028±0.003	0.031±0.003	0.006±0.001
Lung	0.050±0.003	0.061±0.003	0.011±0.001
Fat	0.030±0.004	0.045±0.008	0.006±0.001

[a] Remaining in the body after 72 hr.
[b] Vinyl chloride dissolved in corn oil.
[c] Mean ± SE, five rats per dose.
[d] Not detectable above background.

Adapted from Watanabe et al. 1976a.

Table IV-2 Percentage of ^{14}C Activity per Gram Tissue 72 Hours Following an Inhalation Exposure to (^{14}C) Vinyl Chloride for 6 Hours in Male Sprague-Dawley Rats

	Percentage ^{14}C activity	
	Exposure concentration	
Tissue	10 ppm	1,000 ppm
Liver	0.139±0.009[a] (0.35)(b)	0.145±0.008[a] (9.63)[b]
	0.141±0.009[c]	0.165±0.009[c]
Skin	0.072±0.004 (0.18)	0.115±0.010 (7.64)
	0.073±0.004	0.131±0.011
Carcass	0.048±0.004 (0.12)	0.049±0.004 (3.26)
	0.049±0.004	0.056±0.005
Plasma	0.051±0.001 (0.13)	ND[d]
	0.052±0.001	
Muscle	0.052±0.005 (0.13)	0.038±0.003 (2.52)
	0.053±0.005	0.043±0.003
Lung	0.065±0.007 (0.16)	0.046±0.001 (3.06)
	0.066±0.007	0.052±0.001
Fat	0.026±0.006 (0.07)	ND[d]
	0.026±0.006	
Kidney	0.079±0.003 (0.20)	0.057±0.005 (3.79)
	0.080±0.003	0.065±0.006

[a] Expressed as percentage of total ^{14}C activity per gram of tissue. Uncorrected for expired VC:

$$\frac{\text{dpm per g tissue}}{\text{Total dpm recovered}}$$

Mean ± SE from four rats

[b] Microgram equivalents vinyl chloride per gram of tissue.

[c] Expressed as percentage metabolized ^{14}C activity per gram tissue. Corrected for expired VC:

$$\frac{\text{dpm per gram of tissue}}{\text{Total dpmrecovered - dpm of expired VC}}$$

Mean ± SE from rats.

[d] Not detectable, detection limit for plasma and fat was 3 μg/g of tissue (3 ppm).

Adapted from Watanabe et al. 1976b.

on percent absorption from the gastrointestinal tract, the risk calculations in this document will assume a 100% absorption factor.

B. Metabolism

Metabolism of vinyl chloride occurs primarily by microsomal enzymes in the liver. There is strong evidence that the toxicity of this compound is attributable to its enzymatic oxidation to reactive polar metabolites. Several of these suspected metabolites are strongly mutagenic, but vinyl chloride itself is not (Bartsch and Montesano 1975). Exposure to vinyl chloride leads to the reduction of non-protein sulfhydryl levels in rat liver, suggesting that the metabolites of vinyl chloride conjugate with glutathione and/or cysteine (Hefner et al. 1975a). Hathway (1977) reported *in vitro* depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following administration of vinyl chloride to rats *in vivo*. This suggests that vinyl chloride metabolites may interact with some purine and pyrimidine residues of DNA, providing a possible explanation for the oncogenic properties associated with vinyl chloride.

In a review of the literature, Bartsch and Montesano (1975) report two possible biotransformation schemes—one involving alcohol dehydrogenase (Scheme I) and the other involving the mixed function oxidase system (Scheme II). These are indicated below:

Scheme I: $\mathrm{ClHC{-}CH_2{-}{-}{-}{>}ClH_2C{-}CH_2OH{-}{-}{-}{>}ClH_2C{-}CHO{-}{-}{-}{>}ClH_2C{-}COOH}$

Scheme II: $\mathrm{ClH{-}CH_2{-}{-}{-}{>}[H_2C\overset{O}{-}CHCl]{-}{-}{-}{>}ClH_2C{-}CHO{-}{-}{-}{>}ClH_2C{-}COOH}$

Evidence for biodegradation involving the alcohol dehydrogenase pathway includes data which demonstrates that pretreatment of rats with either ethanol or pyrazole (an inhibitor of alcohol dehydrogenase) inhibits the metabolism of vinyl chloride (Hefner et al. 1975a).

There is also ample evidence that the mixed function oxidase (MFO) system is involved in the metabolism of vinyl chloride. Pretreatment of rats with phenobarbital, which induces the MFO system, also enhanced liver toxicity of vinyl chloride (Jaeger et al. 1974). Rat liver microsomes catalyzed the covalent binding of vinyl chloride metabolites to protein and nucleic acids (Kappus et al. 1975, 1976). Chloroethylene oxide, which is thought to be formed by the MFO system, may be the primary microsomal metabolite capable of alkylating these intra-cellular macromolecules (Laib and Bolt 1977).

Several pathways may be involved in vinyl chloride metabolism, the predominant one depending on dose. Hefner et al. (1975) performed an inhalation study in which rats were exposed to vinyl chloride concentrations ranging from 50.5 to 1,167.0 ppm for 12-months time. The rate of metabolism, as determined by measuring the declining level of vinyl chloride in the chamber atmosphere, was three times greater for seven separate exposures ranging from 50 to 105 ppm than it was for five separate exposures ranging from 220 to 1,167 ppm. This indicated that the predominant pathway at the lower concentrations, probably involving alcohol dehydrogenase, is saturable between 105 and 220 ppm. This group also found evidence that oxidases in the microsomes may be involved in metabolism at high level exposures.

In another study, Bolt et al. (1977) subjected rats to an inspired concentration of ^{14}C-vinyl chloride ranging from 200 to 1,200 ppm in a closed system, and measured the rate of decrease of vinyl chloride levels in the chamber atmosphere. This group calculated that saturation of the vinyl chloride-metabolizing enzymes of the rat occurs at 250 ppm.

C. Excretion

Excretion of ^{14}C activity within 72 hours following a single oral dose of ^{14}C-labeled vinyl chloride (0.05, 1.0 or 100 mg/kg) is shown in Table IV-3 (Watanabe et al. 1976a). As the dose increased, a markedly greater proportion of vinyl chloride was expired unmetabolized, while the percentage of metabolite in the urine decreased substantially. Again, saturation kinetics are suggested. The table also indicates that metabolites of vinyl chloride were predominantly excreted via the urine. Administration of vinyl chloride by inhalation produced almost identical results (Watanable et al. 1976b). Two major metabolites in the urine were identified as indicated in Table IV-4.

Buchter et al. (1980) examined the metabolic elimination of vinyl chloride in Rhesus monkeys. Rhesus monkeys were placed in a closed exposure system into which vinyl chloride was injected, and air samples were taken to determine the decline of vinyl chloride in the gas phase of the system. The results showed that the metabolic elimination of vinyl chloride in Rhesus monkeys is a dose-dependent, saturable process, as it is in rats. Elimination was shown to obey a first-order law of kinetics at air concentrations below

Table IV-3 Percentage of Administered ^{14}C Activity Recovered Following a Single Oral Dose of Vinyl Chloride[a]

	Dose (mg/kg)		
	0.05	1.0	100
Expired:			
As VC	1.43±0.13[b]	2.13±0.22	66.64±0.67
As CO_2	8.96±0.59	13.26±0.47	2.52±0.13
Urine	68.34±0.54	59.30±2.75	10.84±0.95
Feces	2.39±0.52	2.20±0.39	0.47±0.06
Carcass and tissues	10.13±1.93	11.10±0.47	1.83±0.14
Cage wash[c]	0	0.84±0.45	0
Total recovery	91.25±2.47	88.831.98	82.30±0.43

[a] Percentage of dose excreted over 72 hours. Only the ^{14}C activity associated with the expired VC can be attributed to VC per se.

[b] Mean ± SE five rats per dose.

[c] Distilled water wash of metabolism cage at termination of the study.

Adapted from Watanabe et al. 1976a.

Table IV-4 ^{14}C-Containing Urinary Metabolites from Male Sprague-Dawley Rats Given Vinyl Chloride by Gavage[a]

Compound	Dose (mg/kg)		
	0.05(4)[b]	1.0(5)	100(5)
(A) N-acetyl-S-(2-hydroxyethyl-cysteine)	30.4±2.0[c]	36.2±3.9	29.1±2.0
(B) Thiodiglycolic acid	25.6±1.9	23.7±1.1	25.4±0.9
(C) Unidentified	38.6±2.9	34.5±4.6	36.6±2.0
Total	94.6	94.6	91.1

[a] Metabolites were separated and quantitated by high pressure liquid chromatography. Values are expressed as percentage of total urinary radioactivity.
[b] ( ) = Number of animals per dose.
[c] Mean ± SE

Adapted from Watanabe et al. 1976a.

200 to 300 ppm, and at high concentrations the maximal velocity of metabolic elimination of vinyl chloride was about half that of rats when related to kg body weight.

Green and Hathway (1975) measured the excretion of ^{14}C-vinyl chloride administered to rats by intragastric, intravenous (femoral vein), or intraperitoneal routes. Two doses were used: 0.25 mg/kg and 450 mg/kg. The results are shown in Table IV-5. During the first 24 hours after treatment, more than 90% was excreted from the animals irrespective route. Significant differences were noted, however, in the manner of excretion for the 0.25 mg/kg dose. For the intragastric route, 71.5% was excreted in the urine, whereas 99% was exhaled from the lungs when vinyl chloride was administered intravenously. For the intraperitoneal route, 43.2% was exhaled while 41.5% was excreted in the urine. At the higher dose (450 mg/kg), over 90% was exhaled as vinyl chloride in both intragastric and intraperitoneal administered rats. The intragastric values are consistent with the values reported in the oral studies performed by Watanabe et al. (1976a) (see Table IV-3).

Withey and Collins (1976) developed a statistical model for use in equating oral dose levels of vinyl chloride to inhalation exposure levels in rats, using blood level time curves. The authors concluded that "if the total daily liquid intake contained 20 ppm vinyl chloride, then the area generated under the blood level time curve, for rats, would be equivalent to an inhalation exposure of about 2 ppm for 24 hours." Thus, according to this model, inhalation exposure is ten times more efficient than oral exposure.

Table IV-5 EXCRETION OF RADIOACTIVITY IN RATS, GIVEN A SINGLE DOSE OF $[^{14}C]$VINYL CHLORIDE

4 rats were each dosed i.g. with 250 μg of $[^{14}C]$vinyl chloride per kg in corn oil solution, and another 4 rats were each dosed similarly with 450 mg of $[^{14}C]$vinyl chloride per kg. 4 rats were each injected in the femoral vein with 250 μg of $[^{14}C]$vinyl chloride per kg in *N*-(β-hydroxyethyl) lactamide. Four rats were each injected i.p. with 250 μg of $[^{14}C]$vinyl chloride per kg in *N*-(β-hydroxyethyl) lactamide, and another 4 animals were each injected similarly with 450 mg of $[^{14}C]$vinyl chloride.

Size of dose	*Time (h)*	*Radioactivity excreted (% of dose)*[a]											
		Intragastric				*Intravenous*				*Intraperitoneal*			
		Exhaled air		*Urine*	*Faeces*	*Exhaled air*		*Urine*	*Faeces*	*Exhaled air*		*Urine*	*Faeces*
		Vinyl chloride	*CO_2*			*Vinyl chloride*	*CO_2*			*Vinyl chloride*	*CO_2*		
250 μg/kg	0–24	3.7 ± 1.2	12.6 ± 1.1	71.5 ± 5.0	2.8 ± 2.5	99.0 ± 0.8	0.1	0.5	0.1	43.2 ± 4.6	10.3 ± 2.2	41.5 ± 4.8	1.6
	24–48		0.9	3.3	1.6						0.7	1.6	0.2
	48–72			0.3	0.2								
	Total	3.7 ± 1.2	13.5 ± 1.3	75.1 ± 4.2	4.6 ± 3.0	99.0 ± 0.8	0.1	0.5	0.1	43.2 ± 4.6	11.0 ± 1.2	43.1 ± 5.7	1.8
450 mg/kg	0–24	91.9 ± 2.5	0.6	4.5 ± 2.3	0.4					96.2 ± 4.1	0.7	2.5 ± 0.9	0.1
	24–48		0.1	0.8	0.3							0.1	
	48–72			0.1									
	Total	91.9 ± 2.5	0.7	5.4 ± 2.2	0.7					96.2 ± 4.1	0.7	2.6 ± 0.9	0.1

[a] Values shown are the means ± S.D. of those means.

Adapted from Green and Hathway (1975).

V. HUMAN EXPOSURE

Humans may be exposed to vinyl chloride in drinking water, food and air. Detailed information concerning the occurrence of and exposure to vinyl chloride in the environment is presented in another document entitled "Occurrence of Vinyl Chloride in Drinking Water, Food, and Air" (Letkiewicz et al. 1983). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

A. Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to vinyl chloride from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing vinyl chloride. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various vinyl chloride concentrations. The 70-kg male is used for estimating intake.

1. Water

Cumulative estimates of the U.S. populations exposed to various vinyl chloride levels in drinking water from public drinking water systems are presented in Table V-1. The values in the table were obtained using Federal Reporting Data Systems data on populations served by primary water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of vinyl chloride. An estimated 1,922,000 individuals (0.9% of the population of 214,419,000 using public water supplies) are exposed to levels of vinyl chloride in drinking water at or above 1.0 μg/L, while 591,000 individuals (0.3%) are exposed to levels above 5 μg/L. It is estimated that 118,000 individuals are exposed to levels greater than 60 μg/L. Of the approximately 1.3 million people exposed to levels ranging from 1.0 to 5 μg/L, 0.9 million (65%) obtain water from surface water supplies. All exposure to vinyl chloride in drinking water at levels above 5 μg/L is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of vinyl chloride in drinking water. The highest concentrations are expected to occur near sites of polyvinyl chloride production.

Table V-1 Total Estimated Cumulative Population (in Thousands) Exposed to Vinyl Chloride in Drinking Water Exceeding the Indicated Concentration

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of:								
		≥1.0	>5	>10	>20	>30	>40	>50	>60	>70
Groundwater	73,473	1,063	591	118	118	118	118	118	118	0
Surface water	140,946	859	0	0	0	0	0	0	0	0
Total	214,419	1,922	591	118	118	118	118	118	118	0
(% of total)	(100%)	(0.9%)	(0.3%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.0%)

Daily intake levels of vinyl chloride from drinking water were estimated using various exposure levels and the assumptions presented in Table V-2. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.028 µg/kg/day.

An indication of the overall exposure of the total population to vinyl chloride can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of vinyl chloride to which each member of the population is exposed. An explanation of the derivation of these values is presented in Appendix C. Population concentration estimates for vinyl chloride in drinking water were 1.1 x 10^{-7} µg/L x persons (best case), 1.5 x 10^{-7} µg/L x persons (mean best case), 2.3 x 10^{8} µg/L x persons (mean worst case), and 2.3 x 10^{-8} µg/L x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 2.2 x 10^{7} µg/day x persons (best case), 3.0 x 10^{7} µg/day x persons (mean best case), 4.6 x 10^{8} µg/day x persons (mean worst case), and 4.6 x 10^{8} µg/day x persons (worst case) were derived.

2. Diet

No data were obtained on levels of vinyl chloride found in foods in the United States. Therefore, no estimates of the daily intake of vinyl chloride from the U.S. diet could be made.

Table V-2 Estimated Drinking Water Intake of Vinyl Chloride

Exposure level (μg/L)	Persons using supplies exposed to indicated levels		Intake (μg/kg/day)
	Population	% of total population	
≥1.0	1,922,000	0.9%	≥0.028
>5.0	591,000	0.3%	>0.14
>10	118,000	0.1%	>0.29
>50	118,000	0.1%	>1.4
>70	0	0.0%	>2.0

Assumptions: 70-kg man, 2 liters of water/day.

3. Air

Exposure to vinyl chloride in the atmosphere varies from one location to another. The highest level of vinyl chloride reported in the atmosphere was 2,100,000 ng/m^3 (2,100 μg/m^3) (Lillian et al. 1975 cited in Brodzinsky and Singh 1982). High levels, averaging greater than 15,000 ng/m^3 (15 μg/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Bordzinsky and Singh (1982) calculated a median air level of 0.0 ng/m^3 (0.0 μg/m^3) in each of three types of areas: rural/remote, urban/suburban and source dominated.

The monitoring data available are not sufficient to determine regional variations in exposure levels for vinyl chloride.

The daily respiratory intake of vinyl chloride from air was estimated using the assumptions presented in Table V-3 and median and maximum levels for vinyl chloride reported above. The estimates in Table V-3 indicate that the daily vinyl chloride intake from air for adults in rural/remote, urban/suburban, and source dominated areas is 0.0 μg/kg/day. In contrast, the intake calculated using the maximum vinyl chloride level reported is 690 μg/kg/day; few, if any, persons are believed to be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Table V-3 Estimated Respiratory Intake of Vinyl Chloride

Exposure ($\mu g/m^3$)	Intake ($\mu g/kg/day$)
Rural/remote (0.0)	
Urban/suburban (0.0)	0.0
Source dominated (0.0)	
Maximum (2,100)	690

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP 1975).

B. Summary

Table V-4 presents a general view of the total amount of vinyl chloride received by an adult male from air and drinking water. Two separate exposure levels in air and six exposure levels in drinking water are shown in the table. Since no data were obtained on levels of vinyl chloride in foods in the United States, the contribution of vinyl chloride in the diet to total vinyl chloride exposure could not be assessed.

The data presented have been selected from an infinite number of possible combinations of concentrations for the two sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to vinyl chloride at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for vinyl chloride by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of vinyl chloride of 0 $\mu g/m^3$ based on air monitoring data. Assuming an air

Table V-4 Estimated Intake of Vinyl Chloride from the Environment by Adult Males in μg/kg/day (% from Drinking Water)

Concentration in drinking water (ug/l)	Concentration in air: Rural/remote, Urban/suburban, Source dominated (0.0 ug/m^3)	Maximum (2,100 ug/m^3)
0	0.0 (--)	690 (0%)
1.0[a]	0.028 (100%)	690 (<0.01%)
5.0[b]	0.14 (100%)	690 (0.02%)
10[c]	0.29 (100%)	690 (0.04%)
50[d]	1.4 (100%)	690 (0.2%)
70[e]	2.0 (100%)	690 (0.3%)

Intake from each source (see Sections 5.1-5.3):

Water:	1.0 ug/l:	0.028 ug/kg/day
	5.0 ug/l:	0.14 ug/kg/day
	10 ug/l:	0.29 ug/kg/day
	50 ug/l:	1.4 ug/kg/day
	70 ug/l:	2.0 ug/kg/day
Air:	0.0 ug/m^3:	0.0 ug/kg/day
	2,100 ug/m^3:	690 ug/kg/day
Food:	Not included	

[a] 1,922,000 individuals using public drinking water systems are estimated to be exposed to levels ≥ 1.0 ug/l (0.9% of population using public water supplies).

[b] 591,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (0.3% of population using public water supplies).

[c] 118,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l (0.1% of population using public water supplies).

[d] 118,000 individuals using public drinking water systems are estimated to be exposed to levels > 50 ug/l (0.1% of population using public water supplies).

[e] No individuals using public drinking water systems are estimated to be exposed to levels > 70 ug/l.

level of 0 μg/m^3, drinking water would be the predominant source of vinyl chloride exposure at all drinking water levels above 0 μg/L. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of vinyl chloride in drinking water and low concentrations of vinyl chloride in ambient air and food are unknown.

VI. HEALTH EFFECTS IN ANIMALS

A. Acute/Subchronic/Chronic Effects

Acute toxicity tests with vinyl chloride were performed by Patty et al. (1930) of the Bureau of Mines, Department of Commerce. Single exposures of guinea pigs to vinyl chloride gas, 10 percent in air (100,000 ppm), resulted in narcosis and death within 30 to 60 minutes. Inhalation of lower concentrations resulted in ataxia and narcosis. Pathological findings at necropsy were congestion and edema of the lungs and hyperemia of the kidneys and liver. A number of investigators have made similar observations when examining the acute inhalation effects of vinyl chloride in mice, rats, guinea pigs, rabbit, cats and dogs (Peoples and Leake 1933, Lester et al. 1963, Mastromatteo et al. 1960, Haley 1975, Prodan et al. 1975). In animal studies, LC_{50}'s at two hours ranged from 117,500 ppm for mice to 230,800 ppm for rabbits.

Feron et al. (1975) reported a subchronic toxicity study in which vinyl chloride monomer (VCM) dissolved in soybean oil was administered by gavage to male and female Wistar rats, initially weighing 44 g, at doses of 0 (controls), 30, 100 and 300 mg/kg once daily, 6 days per week for 13 weeks. Several hematological, biochemical and organ weight values were significantly ($P<0.05$ or better) different in both mid- and high-dose animals compared to controls. The authors conservatively placed the no-effect level in this study at 30 mg/kg. However, they also estimated that the no-effect level may be higher since it was their opinion that the effects observed with the higher doses were of doubtful toxicological significance.

Marsteller et al. (1975) reviewed and summarized the findings of previous studies on vinyl chloride exposure in laboratory animals. Torkelson et al. (1961) exposed test animals to concentrations ranging from 50 to 500 ppm. Rats exposed to 100 ppm (two hours/day for six months) were judged normal on the basis of appearance, mortality, growth, hematological examination and other factors. A slight increase in the liver weight was observed. Rats, guinea pigs, rabbits and dogs exposed to 50 ppm (7 hours/day, 130 times in 189 days) appeared to be normal in appearance, mortality and growth, and the increase in weight of the rat livers did not occur at this concentration. Basalaev et al. (1972) administered gaseous vinyl chloride to rats and rabbits at a concentration of 0.03 to 0.04 mg/L for four hours/day for six months. Cardiovascular disorders, changes in the bioelectric activity of the hypothalamus, hyperadrenalinemia, osteoporosis and resorption of bone tissue were observed.

Jaeger (1975) conducted experiments with rats to determine the interaction between vinylidene chloride (1,1,-DCE) and vinyl chloride. In this study, hepatotoxicity was measured by the elevation of serum alanine-α-ketoglutarate transaminase (AKT). When fasted rats were exposed to 0.02% (V/V), 1,1-DCE, serum AKT activity was elevated about 50-fold, two hours after the termination of a four-hour inhalation exposure. No elevation was observed when 0.1% vinyl chloride was administered alone. When the two chemicals were administered simultaneously at the levels indicated, no elevation of serum AKT occurred. Thus, the vinyl chloride was protective. These two monomers are used together in the production of vinyl copolymers, and exposure to both agents in the workplace was reported by Kramer and Mutchler (1972).

B. Teratogenicity

John et al. (1977) examined the effects of vinyl chloride inhalation on the fetuses of mice, rats and rabbits. The pregnant animals were exposed seven hours daily to concentrations of 50 or 500 ppm for mice and 500 or 2,500 ppm for rats and rabbits. Mice and rats were exposed on days 6 to 15 of gestation, and rabbits on days 6 to 18. No teratogenic effects were observed at 2,500 ppm in rats and rabbits, except that a greater incidence of dilated ureters were noted in rats. Indeed, vinyl chloride exposure at this level actually decreased the incidence of certain skeletal anomalies in rats compared to controls (e.g., delayed ossification of the bones of the skull, and unfused centers of ossification of the skull and sternebrae). Mice were the most sensitive to vinyl chloride. No teratogenic effects were noted in the fetuses of mice exposed to 50 ppm, but a significantly greater incidence of unfused sternebrae and delayed ossification of sternebrae (no. 5) and bones of the skull were observed among litters of mice exposed to 500 ppm compared to unexposed controls. Embryotoxic effects were not generally noted, but some decrease in fetal body weight and crown-rump length was observed in rats and mice.

Radike (1977) did not observe gross (nonmicroscopic) abnormalities in the offspring of rats exposed for four hours daily on days 9 to 21 of gestation by inhalation of 600 or 6,000 ppm vinyl chloride. A small increase in the incidence of minor skeletal abnormalities, including wavy ribs, extra 14th ribs and delayed calcification of small bones, were observed in the offspring of the exposed animals. The investigators concluded that such a small incidence is difficult to distinguish from a sporadic occurrence, and, therefore, these abnormalities should be considered skeletal variants and not malformations.

Groups of pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to doses of vinyl chloride ranging from 50 to 2,500 ppm by inhalation. Exposure to these concentrations of vinyl chloride did not cause any significant embryonal or fetal toxicity and was not teratogenic in any of the three species tested (John et al. 1981).

C. Mutagenicity

Vinyl chloride is mutagenic in a number of biological systems. The mutagenic action of vinyl chloride appears to be dependent upon its metabolic conversion to chemically reactive metabolites (i.e., chloroethylene oxide, 2-chloroacetaldehyde). The mutagenic effects of vinyl chloride have been demonstrated in: (1) metabolically activated systems using *Salmonella typhimurium* (Bartsch et al. 1975, McCann et al. 1975, Elmore et al. 1976, Rannug et al. 1974, Garro et al. 1976) developed by Ames et al. (1973) in which the genetic indicator refers to histidine prototrophy by base-pair substitutions, or by base-pair insertions or deletions; (2) *Escherichia coli* K12 bioauxotrophic strain with back mutation system arginine + (Greim et al. 1975); (3) several species of yeast inducing forward mutations and gene conversions at specific loci (Loprieno et al. 1976, 1977); (4) germ cells of *Drosophila* (Verburgt and Vogel 1977) and (5) Chinese hamster V79 cells (Huberman et al. 1975). The literature on the mutagenic effects of vinyl chloride was reviewed by Bartsch and Montesano (1975).

The mutagenic activiy of inhaled vinyl chloride (3,000, 10,000 or 30,000 ppm for 6 hours a day for 5 days) was assessed in fertile male CD-1 strain mice with the dominant lethal assay (Anderson et al. 1976). At these concentrations, vinyl chloride was not mutagenic as judged by scoring of post-implantation fetal deaths, pre-implantation egg losses and reduction in fertility. Positive control tests indicated that the dominant lethal effect was expressed in the CD-1 mice used in these experiments.

Anderson and Richardson (1976) conducted a cytogenic study investigating mutagenic effects in the bone marrow cells of rats after exposure to paradichlorobenzene at various dose levels. In this study, benzene and vinyl chloride were used as positive controls. The results of the vinyl chloride control showed that vinyl chloride was effective in producing chromosome damage in rat bone marrow after the multiple exposure regime.

D. Carcinogenicity

Evidence has been accumulated in recent years implicating vinyl chloride as a human and animal carcinogen. The first four cases of human liver angiosarcoma in workers employed by a vinyl chloride plant were reported by Creech and Johnson in 1974. The first experimental data on the carcinogenic effect of vinyl chloride in rats were published by Viola et al. in 1971. Subsequently, preliminary results of an investigation concerned with the oncogenic potential of vinyl chloride in experimental animals were reported (Maltoni and Lefemine 1974). These initial reports spurred a series of retrospective epidemiologic investigations of workers in the vinyl chloride industry and supportive experimental studies in animals. Several comprehensive reviews and symposium proceedings have been published on the subject (e.g., Selikoff and Hammond 1975, Proceedings of the Royal Society of Medicine 1976, USEPA 1975c, Milby 1978).

Viola et al. (1971) conducted animals studies and reported the carcinogenic response of male rats (AR/IRE Wistar strain) exposed to vinyl chloride by inhalation (Table VI-1). Skin tumors were first noted at approximately ten months; tumors in the lungs and bone were observed at about 11 months.

Caputo et al. (1974) exposed male and female rats (A and IRE Wistar strain) by inhalation to various concentrations of vinyl chloride. Carcinomas and sarcomas were observed in all groups except those exposed to 50 ppm (Table VI-2). The data indicate that a dose response relationship exists

Table VI-1 Oncogenic Effects of Inhaled Vinyl Chloride

Conc. VC (ppm) 4 hours/day 5 days/week 12 months	Number rats	Skin epidermoid carcinomas	Lung adenocarcinomas and squamous cell carcinomas	Bones Osteo-chondromas
30,000	26	17	6	5
No treatment	25	--	--	--

Adapted from Viola et al. 1971).

Table VI-2 Incidence of Tumors in Rats and Rabbits Exposed to Vinyl Chloride by Inhalation

(ppm) 4 hours/day 5 days/week 12 months	Number of animals	Liver angiosarcomas cholangiomas	Lung adeno-alveolar carcinomas	Skin squamous cell carcinoma acanthoma	Other
	Rats				
20,000	150	31	21	67	7
10,000	200	16	16	34	8
5,000	200	12	4	20	2
2,000	200	10	8	6	6
500	150	4	--	3	--
50	200	--	--	--	--
No treatment	200	--	--	--	--
	Rabbits				
10,000	40	--	6	12	--
No treatment	20	--	--	--	--

Adapted from Caputo et al. (1974).

at exposures between 50 and 20,000 ppm. Tumors appeared between 8 and 13 months from the beginning of the inhalation treatment. These investigations also exposed rabbits by inhalation to 10,000 ppm vinyl chloride for 15 months (Table VI-2) and reported the occurrence of lung and skin carcinomas.

Recent inhalation studies with albino CD-1 mice and CD rats (Charles River Breeding Lab) confirmed the carcinogenicity of vinyl chloride at concentrations as low as 50 ppm (Lee et al. 1977, 1978). Liver angiosarcomas as well as other forms of cancers were found in both species.

An extensive examination of vinyl chloride in experimental animals was conducted by Maltoni (1981). A summary of these results are presented in Tables VI-3 to VI-19. Vinyl chloride caused tumors in all the animal species tested (i.e., mice, rats and hamsters) both through inhalation and ingestion exposure. A clear-cut dose-response relationship was demonstrated, with carcinogenic effects occurring at exposures as low as 50 ppm. Newborn animals appeared to be especially sensitive to the development of hepatocarcinomas and angiosarcomas and carcinogenic effects on the embryo via the placenta were demonstrated. Table VI-20 indicates the tumor types that were correlated to vinyl chloride exposure in experimental animals.

Maltoni (1981) concluded that vinyl chloride may produce tumors of different types at different sites and that the incidence and relative distribution are greatly influenced by dose, age of the animal, and species and strain of animal used.

Table VI-3

Experiment BT1.*

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	81.7	23.3	11.7 (7/60)	-	5.0 (3/60)	5.0 (3/60)	1.7 (1/60)	8.3 (5/60)	11.7 (7/60)	26.7 (16/60)	5.0 (3/60)	-	5.0 (3/60)
II 6000 ppm	60.0	28.3	22.0 (13/59)	3.4 (2/59)	5.1 (3/59)	6.8 (4/59)	1.7 (1/59)	8.5 (5/59)	5.1 (3/59)	11.9 (7/59)	3.4 (2/59)	1.7 (1/59)	-
III 2500 ppm	63.3	20.0	21.7 (13/60)	-	5.0 (3/60)	3.3 (2/60)	3.3 (2/60)	10.0 (6/60)	6.7 (4/60)	3.3 (2/60)	1.7 (1/60)	-	3.3 (2/60)
IV 500 ppm	51.7	13.3	10.0 (6/60)	-	1.7 (1/60)	1.7 (1/60)	8.3 (5/60)	10.0 (6/60)	-	6.7 (4/60)	1.7 (1/60)	-	1.7 (1/60)
V 250 ppm	30.0	25.0	5.1 (3/59)	1.7 (1/59)	3.4 (2/59)	-	1.7 (1/59)	8.5 (5/59)	-	-	3.4 (2/59)	-	3.4 (2/59)
VI 50 ppm	16.0	36.7	1.7 (1/60)	-	1.7 (1/60)	3.3 (2/60)	-	1.7 (1/60)	-	-	1.7 (1/60)	1.7 (1/60)	3.3 (2/60)
VII No treatment (control)	13.3	43.3	-	-	-	3.4 (2/58)	-	-	-	-	1.7 (1/58)	-	-

*Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm: 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 135 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-4

Experiment BT2.*

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 200 ppm	36.0	21.7	10.0 (12/120)	3.3 (4/120)	0.8 (1/120)	0.8 (1/120)	2.5 (3/120)	5.8 (7/120)	-	3.3 (4/120)	4.2 (5/120)	-	6.0 (6/120)
II 150 ppm	35.0	26.0	5.0 (6/119)	-	-	0.8 (1/119)	-	9.2 (11/119)	-	3.4 (4/119)	3.4 (4/119)	1.7 (2/119)	5.0 (6/119)
III 100 ppm	21.7	27.5	0.8 (1/120)	0.8 (1/120)	-	-	-	8.3 (10/120)	-	0.8 (1/120)	0.8 (1/120)	3.3 (4/120)	3.3 (4/120)
IV No treatment (control)	15.7	21.6	-	-	1.1 (2/185)	-	-	-	-	1.1 (2/185)	1.1 (2/185)	1.6 (3/185)	1.0 (2/185)

*Exposure by inhalation to VC in air at 200, 150, 100 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 143 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-5

Experiment BT6.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 30,000 ppm	100.0	50.0	30.0 (18/60)	1.7 (1/60)	1.7 (1/60)	5.0 (3/60)	1.7 (1/60)	-	1.7 (1/60)	58.3 (35/60)	1.7 (1/60)	18.3 (11/60)	3.3 (2/60)

[a] Exposure by inhalation to VC in air at 30,000 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 17 weeks old. Results after 68 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-6

Experiment BT9.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 50 ppm II	44.3	41.7	4.8 (14/294)	2.7 (8/294)	3.1 (9/294)	3.7 (11/294)	-	0.3 (1/294)	-	3.1 (9/294)	1.0 (3/294)	0.4 (1/294)	21.7 (62/294)
No treatment (control)	23.0	24.0	-	-	-	-	-	-	-	-	-	1.0 (1/98)	10.2 (10/98)

[a] Exposure by inhalation to VC in air at 50 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 142 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-7

Experiment BT15.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 25 ppm	33.3	58.3	4.2 (5/120)	0.8 (1/120)	–	2.5 (3/120)	–	0.8 (1/120)	–	3.3 (4/120)	–	–	15.0 (17/120)
II 10 ppm	31.7	53.3	0.8 (1/119)	–	1.7 (2/119)	2.5 (3/119)	–	–	–	1.7 (2/119)	–	–	17.6 (21/119)
III 5 ppm	35.8	55.0	–	–	–	–	–	–	–	0.8 (1/119)	0.8 (1/119)	–	18.5 (22/119)
IV 1 ppm	22.5	44.2	–	–	–	–	–	–	–	0.8 (1/118)	0.8 (1/118)	–	12.7 (15/118)
V No treatment (control)	23.3	37.5	–	–	–	0.8 (1/120)	–	–	–	1.7 (2/120)	–	–	5.8 (7/120)

[a] Exposure by inhalation to VC in air at 25, 10, 5, 1 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 147 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-8

Experiment BT3.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	45.0	20.0	-	-	-	1.7 (1/58)	1.7 (1/58)	1.7 (1/58)	15.5 (9/58)	15.5 (9/58)	8.6 (5/58)	1.7 (1/58)	1.7 (1/58)
II 6000 ppm	53.3	25.0	1.7 (1/60)	-	-	3.3 (2/60)	1.7 (1/60)	1.7 (1/60)	20.0 (12/60)	15.0 (9/60)	8.3 (5/60)	3.3 (2/60)	1.7 (1/60)
III 2500 ppm	41.7	35.0	1.7 (1/60)	-	-	-	3.3 (2/60)	3.3 (2/60)	8.3 (5/60)	11.7 (7/60)	3.3 (2/60)	-	6.7 (4/60)
IV 500 ppm	15.0	35.0	1.7 (1/60)	-	-	-	-	-	-	1.7 (1/60)	-	-	5.0 (3/60)
V 250 ppm	21.7	25.0	-	1.7 (1/59)	-	1.7 (1/59)	-	10.2 (6/59)	-	1.7 (1/59)	-	5.1 (3/59)	1.7 (1/59)
VI 50 ppm	18.3	25.0	-	1.7 (1/58)	-	1.7 (1/58)	-	5.2 (3/58)	-	-	1.7 (1/58)	-	1.7 (1/58)
VII No treatment (control)	14.7	20.0	-	-	0.5 (1/190)	-	-	-	-	1.0 (2/190)	0.5 (1/190)	-	2.6 (5/190)

[a] Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 17 weeks. Sprague-Dawley rats, M and F, 12 weeks old. Results after 156 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-9

Experiment BT10.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mar MT
I 10,000 ppm	33.3	41.7	0.8 (1/118)	-	-	0.8 (1/118)	0.8 (1/118)	-	-	7.6 (9/118)	-	2.5 (3/118)	11.0 (13/11
II 6000 ppm	30.0	45.0	-	0.8 (1/120)	-	1.7 (2/120)	-	0.8 (1/120)	0.8 (1/120)	7.5 (9/120)	-	1.7 (2/120)	10.8 (13/120
III 10,000 ppm	35.8	45.0	0.8 (1/119)	1.7 (2/119)	-	0.8 (1/119)	-	-	-	7.6 (9/119)	2.5 (3/119)	2.5 (3/119)	13.4 (16/119
IV 6000 ppm	30.8	39.2	2.5 (3/118)	-	1.7 (2/118)	-	-	-	-	4.2 (5/118)	3.4 (4/118)	1.7 (2/118)	9.3 (11/118
V 10,000 ppm	41.7	45.0	0.8 (1/119)	1.7 (2/119)	-	0.8 (1/119)	-	0.8 (1/119)	0.8 (1/119)	6.7 (8/119)	0.8 (1/119)	0.8 (1/119)	16.8 (20/119
VI 6000 ppm	33.3	50.8	0.8 (1/120)	1.7 (2/120)	0.8 (1/120)	-	1.7 (2/120)	0.8 (1/120)	-	7.5 (9/120)	-	0.8 (1/120)	10.0 (12/120
VII No treatment (control)	16.6	41.0	-	-	-	0.4 (1/227)	-	-	-	-	0.9 (2/227)	2.2 (5/227)	7.5 (17/22

[a]Exposure by inhalation to VC in air at 10,000, 6000, ppm; 4 hr/day, 5 days/week, for 5 weeks (groups I and II) or 1 hr/day, 4 days/week, for 25 weeks (groups III and IV) or 4 hr/day, once weekly, for 25 weeks (groups V and VI) (100 hr). Sprague-Dawley rats, M and F, 13 weeks old. Results after 154 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-10

Experiment BT5.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 10,000 ppm	6.7	36.7	–	–	–	–	–	–	–	3.3 (1/30)	–	–	–
II 6000 ppm	6.7	23.3	–	–	–	–	–	–	–	–	–	–	–
III 10,000 ppm	29.6	22.2	–	–	–	–	–	5.9 (3/51)	–	9.8 (5/51)	–	2.0 (1/51)	2.0 (1/51)
IV 6000 ppm	21.9	46.9	–	–	–	3.1 (1/32)	–	–	–	9.4 (3/32)	3.1 (1/32)	3.1 (1/32)	6.2 (2/32)

[a] Exposure by inhalation to VC in air at 10,000, and 6000 ppm of breeders; 4 hr/day for 1 week (from 12th to 18th day of pregnancy). Sprague-Dawley rats, M and F, 19 weeks old (breeders). Breeders (groups I and II) and offsprings (groups III and IV). Results after 143 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-11

Experiment BT14.*

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mammary MT
I 10,000 ppm (breeders)	16.7	66.7	–	–	–	–	–	–	–	–	–	–	–
II 6000 ppm (breeders)	–	–	–	–	–	–	–	–	–	–	–	–	–
III 10,000 ppm (newborn)	100.0	55.5	34.1 (15/44)	–	–	6.8 (3/44)	45.4 (20/44)	–	–	2.3 (1/44)	2.3 (1/44)	–	–
IV 6000 ppm (newborn)	109.3	58.1	40.5 (17/42)	2.4 (1/42)	2.4 (1/42)	2.4 (1/42)	47.6 (20/42)	–	–	4.8 (2/42)	4.8 (2/42)	–	2.4 (1/42)

*Exposure by inhalation to VC in air at 10,000 and 6000 ppm, 4 hr/day, 5 days/week, for 5 weeks (from 1 day to 5 weeks of age). Sprague-Dawley rats, M and F, 21 weeks old (breeders) (groups I and II) and newborn (groups III and IV). Results after 124 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-12

. Experiment BT7.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %									
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac
I 10,000 ppm	50.0	10.0	29.6 (8/27)	–	–	–	–	3.7 (1/27)	11.1 (3/27)	7.4 (2/27)	–	–
II 6000 ppm	53.3	20.0	11.5 (3/26)	7.7 (2/26)	3.8 (1/26)	3.8 (1/26)	7.7 (2/26)	7.7 (2/26)	3.8 (1/26)	7.7 (2/26)	–	–
III 2500 ppm	26.7	13.3	12.0 (3/25)	–	4.0 (1/25)	–	4.0 (1/25)	–	4.0 (1/25)	–	4.0 (1/25)	–
IV 500 ppm	30.0	10.0	10.7 (3/28)	3.6 (1/28)	–	–	–	7.1 (2/28)	–	–	–	–
V 250 ppm	13.3	16.7	3.7 (1/27)	–	3.7 (1/27)	3.7 (1/27)	–	–	–	–	3.7 (1/27)	–
VI 50 ppm	16.7	6.7	–	–	–	–	–	3.6 (1/28)	–	–	–	–
VII No treatment (control)	15.0	15.0	–	–	2.6 (1/38)	–	–	–	–	–	–	–

[a] Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 52 weeks. Wistar rats, M, 11 weeks old. Results after 165 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-13

Experiment BT17.*

Group and concentration	Tumors/100 animals		Animals with tumors, %									
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac
I 1 ppm II	24.2	29.2	–	1.0 (1/99)	3.0 (3/99)	5.0 (5/99)	1.0 (1/99)	–	–	2.0 (2/99)	–	–
No treatment (control)	20.0	18.5	–	–	–	–	–	–	–	3.2 (3/94)	–	1.1 (1/94)

*Exposure by inhalation to VC in air at 1 ppm; 4 hr/day, 5 days/week, for 52 weeks. Wistar rats, M, 13 weeks old. Results after 134 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-14

Experiment BT4.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %						
	MT	BT	LAS	LA	ELAS	ELA	Lung T	Mammary Ca	Skin EpT	Fore-stomach Pa&Ac
I 10,000 ppm	50.0	98.3	17.8 (10/56)	10.7 (6/56)	1.8 (1/56)	7.1 (4/56)	82.1 (46/56)	23.2 (13/56)	7.1 (4/56)	1.8 (1/56)
II 6000 ppm	56.7	100.0	21.7 (13/60)	11.7 (7/60)	1.7 (1/60)	5.0 (3/60)	78.3 (47/60)	13.3 (8/60)	11.7 (7/60)	1.7 (1/60)
III 2500 ppm	58.3	90.0	27.1 (16/59)	8.5 (5/59)	13.5 (8/59)	1.7 (1/59)	67.8 (40/59)	13.5 (8/59)	6.8 (4/59)	1.7 (1/59)
IV 500 ppm	58.3	103.3	23.3 (14/60)	8.3 (5/60)	11.7 (7/60)	5.0 (3/60)	83.3 (50/60)	13.3 (8/60)	3.3 (2/60)	–
V 250 ppm	63.3	98.3	30.0 (18/60)	18.3 (11/60)	5.0 (3/60)	5.0 (3/60)	68.3 (41/60)	20.0 (12/60)	1.7 (1/60)	1.7 (1/60)
VI 50 ppm	28.3	23.3	1.7 (1/60)	1.7 (1/60)	1.7 (1/60)	8.3 (5/60)	10.0 (6/60)	20.0 (12/60)	– –	1.7 (1/60)
VII No treatment (control)	14.7	14.7	–	–	0.7 (1/150)	0.7 (1/150)	10.0 (15/150)	0.7 (1/150)	1.3 (2/150)	–

[a] Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 30 weeks. Swiss mice, M and F, 11 weeks old. Results after 81 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-15

Experiment BT8.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELA	Hepa-tomas	Cholan-gio-Ca	Cholan-giomas	Acoustic Duct EpT	Skin EpT	Mela-nomas	Fore-stomach Pa&Ac	Leukemias[b]
I 10,000 ppm	50.0	73.3	-	3.3 (1/30)	6.7 (2/30)	-	6.7 (2/30)	13.3 (4/30)	3.3 (1/30)	23.3 (7/30)	3.3 (1/30)	33.3 (10/30)	16.7 (5/30)
II 6000 ppm	40.0	63.3	3.3 (1/30)	3.3 (1/30)	-	3.3 (1/30)	6.7 (2/30)	16.7 (5/30)	6.7 (2/30)	3.3 (1/30)	6.7 (2/30)	33.3 (10/30)	20.0 (6/30)
III 2500 ppm	43.3	103.3	-	6.7 (2/30)	-	-	-	26.7 (8/30)	3.3 (1/30)	10.0 (3/30)	3.3 (1/30)	56.7 (17/30)	30.0 (9/30)
IV 500 ppm	53.3	63.3	6.7 (2/30)	-	3.3 (1/30)	-	-	20.0 (6/30)	10.0 (3/30)	23.3 (7/30)	-	30.0 (9/30)	16.7 (5/30)
V 250 ppm	30.0	43.3	-	-	3.3 (1/30)	-	-	20.0 (6/30)	-	10.0 (3/30)	3.3 (1/30)	13.3 (4/30)	20.0 (6/30)
VI 50 ppm	50.0	40.0	-	-	-	-	-	23.3 (7/30)	-	30.0 (9/30)	3.3 (1/30)	10.0 (3/30)	20.0 (6/30)
VII [c]No treatment (control)	20.0	46.7	-	-	-	-	-	36.7 (22/60)	-	5.0 (3/60)	-	5.0 (3/60)	13.3 (8/60)

[a] Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 30 weeks. Golde hamsters, M, 11 weeks old. Results after 109 weeks (end of experiment).

[b] Latency time in weeks: Group I, 16.7; Group II, 27.2; Group III, 30.8; Group IV, 19.0; Group V, 22.5; Group VI, 35.3; Group VII, 36.5.

Adapted from Maltoni, 1981

Table VI-16

Experiment BT11.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 50.00 mg/kg	38.7	35.0	21.2 (17/80)	3.7 (3/80)	2.5 (2/80)	2.5 (2/80)	-	2.5 (2/80)	-	1.2 (1/80)	1.2 (1/80)	2.5 (2/80)	5.0 (4/80)
II 16.65 mg/kg	30.0	17.5	12.5 (10/80)	-	-	-	-	3.7 (3/80)	-	2.5 (2/80)	-	1.2 (1/80)	7.5 (6/80)
III 3.33 mg/kg	10.0	25.0	-	-	2.5 (2/80)	1.2 (1/80)	-	-	-	-	-	-	3.7 (3/80)
IV Olive oil (control)	13.7	22.5	-	-	-	-	-	-	-	1.2 (1/80)	1.2 (1/80)	-	5.0 (4/80)

[a] Exposure by ingestion (stomach tube) of VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 136 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-17

Experiment BT27.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 1.0 mg/kg	24.7	35.3	2.0 (3/149)	–	0.7 (1/149)	–	0.7 (1/149)	–	–	3.3 (5/149)	–	2.0 (3/149)	8.0 (12/149)
II 0.3 mg/kg	13.3	28.0	0.7 (1/148)	0.7 (1/148)	–	–	0.7 (1/148)	–	–	–	0.7 (1/148)	1.3 (2/148)	2.7 (4/148)
III 0.03 mg/kg	18.0	31.3	–	–	–	–	–	–	–	–	0.7 (1/150)	0.7 (1/150)	9.3 (14/150)
IV Olive oil (control)	16.0	28.7	–	–	–	–	–	–	–	0.7 (1/150)	–	1.3 (2/150)	4.7 (7/150)

[a] Exposure by ingestion (stomach tube) of VC in olive oil at 1.0, 0.3, 0.03 mg/kg body weight, once daily, 4-5 days/week, for 59 weeks. Sprague-Dawley rats, M and F, 10 weeks old. Results after 136 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-18

Experiment BT12.*

Group and dose	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 4.25 mg × 4	13.8	25.0	–	–	–	–	–	–	–	–	–	1.8 (1/56)	1.8 (1/56)
II 4.25 mg × 3	16.7	28.3	–	–	1.9 (1/53)	–	–	–	–	–	–	1.9 (1/53)	1.9 (1/53)
III 4.25 mg × 2	11.7	18.3	–	–	1.8 (1/56)	–	–	–	–	–	1.8 (1/56)	–	5.3 (3/56)
IV 4.25 mg × 1	20.0	35.0	–	–	–	1.8 (1/55)	–	–	–	1.8 (1/55)	–	3.6 (2/55)	3.6 (2/55)
V Olive oil (control)	8.3	51.7	–	–	–	–	–	–	–	–	–	3.6 (2/55)	–

*Exposure by intraperitoneal injection of VC, 4.25 mg in olive oil (1 ml), 4, 3, 2 times, at two month intervals or once only. Sprague-Dawley rats, M and F, 17 weeks old. Results after 144 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-19

Experiment BT13.[a]

Group and dose	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepa-tomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Fore-stomach Pa&Ac	Mam-mary MT
I 4.25 mg	16.0	17.3	-	-	-	-	-	1.3 (1/75)	-	-	-	-	4.0 (3/75)
II Olive oil (control)	13.3	26.7	-	-	-	1.3 (1/75)	-	-	-	1.3 (1/75)	-	-	1.3 (1/75)

[a] Exposure by subcutaneous injection of VC, 4.25 mg, in olive oil (1 ml), single dose. Sprague-Dawley rats, M and F, 21 weeks old. Results after 145 weeks (end of experiment).

Adapted from Maltoni, 1981

Table VI-20 Tumors Presently Correlated to VC Exposure (by Inhalation) on Experimental Rodents

Species	Angiosarcomas of liver	Tumors of brain	Tumors of lung	Lymphomas and leukemias	Hepatomas	Angiosarcomas and angiomas of other sites	Nephroblastomas	Sebaceous cutaneous carcinomas	Other cutaneous epithelial tumors	Mammary carcinomas	Forestomach papillomas and acanthomas	Melanomas
Rat	+	+			+	+	+	+	(+)	+	+	
Mouse	+		+			+			(+)	+	(+)	
Hamster	+			(+)		(+)			(+)		+	(+)

Adapted from Maltoni, 1981

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Abbreviations used in tables[a]

Abbreviation	
T	Tumor
Ca	Carcinoma
Ep T	Epithelioma
Pa	Papilloma
Ac	Acanthoma
Ad	Adenoma
Ad ↑	Adenoma in malignant transformation
MT	Malignant tumors (total if not otherwise specified)
BT	Benign tumors (total if not otherwise specified)
LAS	Liver angiosarcoma
LA	Liver angioma
ELAS	Extra-liver angiosarcoma
ELA	Extra-liver angioma
Nephro-BL	Nephroblastoma
Neuro-BL	Neuroblastoma
A	Angioblastic hyperplasia in liver
A ↑	Angioblastic dysplasia in liver
Neop. nod.	Neoplastic nodules of liver
Nod. hyp.	Nodular hyperplasia of liver
Dif. hyp.	Diffused hyperplasia of liver
++	Marked
+++	Very marked

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[a] The incidence of total malignant and benign tumours is given as the total number of tumors per 100 animals (one animal may bear more than one malignant or benign tumor) on the basis of the tumors observed among the animals alive, when the first tumor was observed in the experiment.

The incidence of specific tumour is given, as percent of the animals bearing the tumor considered, referred to the animals alive when the first tumor was observed (in parentheses).

Adapted from Maltoni, 1981

A recently completed study by Feron et al. (1981) examined the oral toxicity of vinyl chloride in Wistar rats. This study was carried out over the lifespan of the rats, and consisted of incorporating PVC powder containing a high content of vinyl chloride monomer (VCM) in the diet, or using gastric intubation of a 10% VCM in soybean oil. The VCM doses (actual exposures) were 0, 1.7, 5.0 and 14.1 mg/kg bw through the diet or 300 mg/kg bw by gastric intubation. The results showed that rats exposed to VCM at levels of 5.0 mg/kg bw day or more demonstrated hepatic angiosarcomas, pulmonary angiosarcomas, and at the higher levels, a few primary extrahepatic abdominal angiosarcomas. At the lowest exposure level of 1.7 mg vinyl chloride monomer/kg bw/day, liver-cell tumors and an increased incidence of foci of cellular alteration were noted (Tables VI-21 and VI-22).

Feron et al. (1981) concluded that VCM is a carcinogen when administered by the oral route, and that the tumor response seems to shift from the exclusive development of angiosarcomas at very high levels to the exclusive induction of hepatocellular tumors at low levels of exposure. Feron et al. have also initiated a similar lifespan oral carcinogenicity study with vinyl chloride in rats, using three different dose levels (0.017, 0.17 and 1.7 mg VCM/kg bw day) and two control groups.

Til et al. (1983) examined the oral carcinogenicity of VCM in a lifespan study (149 weeks) with five groups of Wistar rats, each consisting of 100 males and 100 females, except for the top-dose group which comprised 50 males and 50 females. VCM was administered by incorporating PVC powder with a high VCM content into the diet. The diet was provided daily for a period of four

Table VI-21 Type and Incidence of Treatment-Related Histopathological Changes in the Liver of Rats Exposed Orally to VCM

Type of change¶	Treatment group (mg VCM/kg/day)...	Incidence of change									
		Males					Females				
		0	1.7	5.0	14.1	300†	0	1.7	5.0	14.1	300†
	Animals killed after 26 wk										
	No. of rats examined...	10	§	—	10	9	10	—	—	10	10
Clear-cell foci		0	—	—	1	1	0	—	—	5**	2
	Animals killed after 52 wk										
	No. of rats examined...	9	—	—	10	9	9	—	—	10	8
Clear-cell foci		1	—	—	8**	0	0	—	—	8**	0
Basophilic foci		0	—	—	0	0	0	—	—	4	1
Eosinophilic foci		0	—	—	2	0	0	—	—	5**	0
Neoplastic nodule		0	—	—	1	0	0	—	—	2	0
Hepatocellular carcinoma		0	—	—	1	0	0	—	—	1	0
Cystic proliferation of bile ducts		0	—	—	0	0	0	—	—	4*	0
	Animals found dead or killed in extremis or terminally										
	No. of rates examined...	55	58	56	59	55	57	58	59	57	54
Clear-cell foci		0	9**	16***	21***	9	4	24***	22***	36***	10
Basophilic foci		8	18	21*	22**	12	0	33***	17	28***	19
Eosinophilic foci		3	23***	27***	33***	11	8	35***	20*	29***	6
Neoplastic nodule		0	1	7**	23***	3	2	26**	39***	44***	2
Hepatocellular carcinoma		0	1	2	8**	1	0	4	19**	29***	0
Angiosarcoma		0	0	6*	27***	27	0	0	2	9**	29

Table VI-21 - continued

Proliferation of atypical sinusoidal cells only	2	0	4	7	6	4	6	3	4	7
Extensive necrosis	4	4	8	23***	21	5	6	19***	27***	24
Cysts	2	3	4	16***	3	9	30***	41***	49***	3
Liver-cell polymorphism	4	16*	28***	42***	36	34	51*	38	41	41
Centrilobular degeneration	0	0	0	1	1	1	2	3	1	18
Focal haematopoiesis	0	1	0	10**	8	1	3	1	6	12

¶Specific hepatocellular lesions were classified according to Squire & Levitt (1975).

†The figures of this group were not evaluated statistically because no corresponding control group was included in the study.

§Not examined.

The initial number of animals was 60/sex/group. A number of rats could not be examined because of cannibalism c advanced autolysis.

Values marked with asteriks differ significantly from those of the controls according to the chi-square test: *p<0.05; **p<0.01; ***p<0.001.

Adapted from Feron et al. 1981.

Table VI-22 Site, Type and Incidence of Tumors in Organs Other than the Liver in Rats Exposed Orally to VCM for Over 2 to 5 Years

Site and type of tumour	Treatment group (mg VCM/kg/day)...	Incidence of tumours									
		Males					Females				
		0	1.7	5.0	14.1	300†	0	1.7	5.0	14.1	300
	Effective no. of rats...	55	58	56	59	55	57	58	59	57	54
	No. of rats with primary tumours...	38	50	49	52	44	54	56	55	57	47
Lungs											
Angiosarcoma		0	0	4*	19***	19	0	0	1	5*	23
Adenoma		0	0	0	0	1	0	0	0	0	0
Zymbal glands											
Squamous-cell carcinoma		0	0	2	0	1	0	0	0	0	1
Adenoma		0	0	0	0	0	0	0	0	0	1
Abdomen											
Mesothelioma		3	1	7	8	1	1	6*	3	3	0
Angiosarcoma		0	0	0	0	1	0	0	0	2	1
Fibarosarcoma		0	0	0	3	0	1	2	0	0	0
Osteosarcoma		0	0	0	0	1	0	0	0	1	0
Sarcoma		0	0	3	1	0	0	0	1	0	0
Reticulum-cell sarcoma		0	1	0	0	1	0	0	0	0	0
'Schwann-cell tumour'		0	0	0	0	0	0	1	0	0	0
Unclassified		0	0	0	0	0	2	0	0	0	0
Spleen											
Haemangioendotheliosarcoma		0	1	0	0	0	0	0	0	0	0
Lymphosarcoma		0	0	0	0	0	0	0	0	0	1
Nose											
Squamous-cell carcinoma		0	0	0	1	0	0	0	0	0	0
Brain											
Granular-cell myoblastoma		1	1	0	0	0	0	1	0	0	0
Oligodendroglioma		1	0	0	0	0	0	0	0	0	0
Plexus papilloma		0	0	0	0	0	0	1	0	0	0
Glial-cell tumour		0	0	2	0	1	0	0	0	0	0
Ependymoma		0	0	0	1	0	0	0	0	0	0
Mesodermal tumour		0	0	1	0	0	0	0	0	0	0
Pancreas											
Adenocarcinoma		0	0	0	0	0	1	2	1	0	0
Thorax											
Mesothelioma		1	0	0	0	0	0	0	0	0	0
Thyroid											
Parafollicular-cell adenoma		4	12*	10	3	3	7	10	3	2	0
Parafollicular-cell carcinoma		1	0	1	0	0	0	0	0	0	0
Follicular-cell adenoma		0	0	0	1	0	1	0	0	1	0

TABLE VI-22 (continued)

Site and type of tumour	Treatment group (mg VCM/kg/day)	Incidence of Tumours									
		Males					Females				
		0	1.7	5.0	14.1	300[†]	0	1.7	5.0	14.1	300[†]
Adrenals											
Cortical adenoma		18	25	17	10	9	26	30	20	17	14
Phaeochromocytoma		11	21	8	4	6	2	1	2	0	2
Pituitary											
Adenoma		12	25**	6	2**	0	14	16	10	5*	3
Carcinoma		1	0	1	0	0	3	0	2	0	0
Blood											
Leukemia		1	0	1	1	3	1	2	1	0	1
Heart											
Endocardial disease[§]		2	0	2	2	1	1	0	0	0	1
Haemangioendotheliosarcoma		1	0	0	0	0	0	0	0	0	0
Kidneys											
Nephroblastoma		1	0	0	1	0	0	0	0	0	0
Clear-cell tumour		0	0	0	0	0	0	0	0	1	0
Lipomatous tumour		0	0	1	0	0	0	0	0	0	0
Unclassified epithelial tumour		0	0	0	0	0	1	0	0	0	0
Thymus											
Fibrosarcoma		0	1	0	0	0	0	0	0	0	0
Reticulum-cell sarcoma		0	0	0	0	1	0	1	1	0	0
Mesenteric lymph nodes											
Reticulum-cell sarcoma		0	0	0	0	1	0	0	0	0	0
Skin											
Squamous-cell carcinoma		2	3	3	1	0	0	0	0	1	0
Subcutis											
Fibroma		2	1	1	1	1	3	3	1	0	0
Fribrosarcoma		0	1	1	0	0	1	1	0	0	0
Mesenchymal tumour		0	0	0	0	0	1	0	0	0	0
Skeletal muscle											
Rhabdomyosarcoma		0	0	0	1	1	1	0	0	0	0

TABLE VI-22 (continued)

Site and type of tumour	Treatment group (mg VCM/kg/day)	Incidence of Tumours									
		Males					Females				
		0	1.7	5.0	14.1	300†	0	1.7	5.0	14.1	300†
Skull											
Osteoma		1	0	0	0	0	0	0	0	0	0
Mesenchymal tumour		0	0	0	0	0	0	1	0	0	0
Ear region											
Adenocarcinoma of unknown origin		0	0	1	0	0	0	0	0	0	0
Urinary bladder											
Unclassified epithelial tumour		0	0	1	0	0	0	0	0	0	0
Preputial glands											
Squamous-cell carcinoma		0	0	1	0	0	0	0	0	0	0
Mammary glands											
Adenoma		0	0	0	0	0	0	0	0	2	0
Fibroadenoma		0	0	0	0	0	21	25	12**	4**	7
Adenocarcinoma		0	1	0	2	0	3	2	4	7	7
Anaplastic carcinoma		0	0	0	0	0	0	0	1	0	0
Testes											
Interstitial-cell tumour		3	0	0	1	1					
Uterus											
Adenocarcinoma							6	3	1	1	0
Malignant fibroadenomatous tumour							0	1	0	0	0
Leiomyoma							0	0	1	0	0
Cervix											
Mesenchymal type of tumour							2	0	1	0	0
Adenocarcinoma							0	1	0	0	0
Ovaries											
Theca-cell tumour							0	0	1	0	0

‡A small number of primary liver tumours unrelated to treatment were found in several groups. These tumours wer one Kupffer-cell sarcoma, three reticulum-cell sarcomas, two fibrosarcomas, one haemangioendothelioma and one mesenchymal tumour.

†The figures for this group were not evaluated statistically, because no corresponding control group was included in the study.

§In several cases the neoplastic character of the lesion was doubtful.

Values marked with asteriks differ significantly from those of the controls according to the chi-square test: *P<0.05; **P<0.01; ***P<0.001.

Adapted from Feron et al. 1981)

consecutive hours, and food was withdrawn during the other 20 hours. Oral VCM exposure levels were 0 (control), 0.014, 0.13 and 1.3 mg VCM/kg bw/day. An extra control group of 100 rats/sex was housed in a separate room.

Additional groups of 10 male and 10 female rats, each receiving the same treatment as the main groups, were used for determinations of glutathione levels in the liver after 9 and 18 months. Observations were made of general appearance, mortality, growth, food intake, thrombocyte count, prothrombin time, glutathione levels in the liver, gross pathology and microscopic pathology of the liver and of all grossly visible tumors or presumable tumors in the abdominal cavity, Zymbal gland and the mammary glands.

General health, behavior, body weight and food intake were not adversely affected by the test substance. In the second half of the experimental period, mortality in the extra control group was higher than in all other groups. This was most probably due to a high incidence of chronic respiratory disease in the extra control group. In the final stage of the study, the mortality in the top-dose group was slightly higher than in the lower dose groups and the controls. Thrombocyte count, prothrombin time and liver glutathione levels did not show treatment-related differences among the groups.

A clearly higher incidence of grossly visible, tumorous, liver nodules was found in both males and females of the top-dose group than in any of the other groups. Moreover, in females of the top-dose group the incidence of hepatic cysts was considerably higher than in controls.

Microscopic examination of the liver revealed increased incidences of liver-cell polymorphism, hepatic cysts, foci of cellular alteration, neoplastic nodules and hepatocellular carcinomas in the top-dose group as compared to the control group. One mid-dose female had a hepatocellular carcinoma and neoplastic nodules were found in one low-dose female and in one mid-dose female. A control female was diagnosed with hepatocellular carcinoma. A hepatic angiosarcoma was found in one male and two females of the top-dose group, but no such tumors were encountered in any of the other groups. The number of animals bearing foci of cellular alteration in the liver was also statistically significantly increased in females of the mid-dose group as compared to controls. In addition, in females but not in males, the incidence of basophilic foci of cellular alteration in the liver was statistically significantly higher in both the low- and the mid-dose group than in the control group. Details of the histopathological examination of liver are in Table VI-23.

There was no evidence of VCM-feeding affecting the incidence of abdominal mesotheliomas or the type and incidence of mammary gland tumors (Table VI-24). No Zymbal gland tumor was found.

Table VI-23 Type and Incidence of Histopathological Changes in the Liver

Type of changes[1]	Incidence of changes									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
Number of animals examined	99	99	99	49	100	98	100	96	49	99
1. Foci of cellular alteration										
a. clear cell foci										
I one or a few	12	8	8	16**	5	4	5	3	13***	1
II several	0	0	0	3*	0	0	0	0	6***	0
b. basophilic foci										
I one or a few	4	2	3	8*	0	9	20*	26***	19***	4
II several	0	0	0	0	0	0	1	0	2	0
c. mixed cell foci										
I one or a few	0	1	2	2	0	6	6	4	8*	0
d. eosinophilic foci										
I one or a few	1	1	2	1	0	0	0	1	10***	2
All type of foci:										
Total	17	12	15	30	5	19	32	34	58	7
Number of foci-bearing animals	16	12	15	23***	5**	19	27	31*	32***	7**

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Table VI-23 - continued

Type of changes	Incidence of changes									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
2. Neoplastic nodules										
a. one	0	0	0	1	0	0	1	1	9***	0
b. a few	0	0	0	2	0	0	0	0	1	0
3. Hepatocellular carcinoma	0	0	0	3*	0	1	0	1	3	0
4. Angiosarcoma	0	0	0	1	0	0	0	0	2	0
5. Liver-cell polymorphism										
a. slight	27	23	26	19	12**	46	41	49	23	38
b. moderate	4	4	7	10**	1	14	13	8	15*	15
c. severe	1	1	1	3	0	2	3	4	9***	3
6. Prominent sinusoidal cells										
a. slight	1	1	1	0	1	4	9	3	1	6
b. moderate/marked	1	2	1	1.	0	3	8	5	7	0
7. Cysts										
a. one	1	0	1	0	0	3	2	4	1	1
b. a few	4	4	3	4	1	11	11	12	7	2**
c. many	0	0	0	0	0	3	4	9	24***	1
8. Bile duct proliferation										
a. slight	37	26	35	14	21**	27	23	36	18	14*
b. moderate	9	9	8	3	1**	11	6	10	2	3*
c. severe	2	0	0	0	1	1	2	1	1	4

Table VI-23 - continued

Type of changes	Incidence of changes									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
9. Cholangiofibrosis										
a. slight	33	19*	20*	15	23	16	13	17	15	2***
b. moderate	2	6	8*	2	1	6	2	4	0	0*
10. Periportal fibrosis										
a. slight	1	2	2	3	5	0	0	0	0	1
b. moderate	2	0	0	0	2	0	0	0	0	0
11. Periportal/centrolobular infiltrates of mononuclear cells										
a. slight	14	10	8	3	7	3	2	1	2	4
b. moderate	1	1	1	0	0	0	0	2	0	0
c. severe	0	1	1	0	0	0	0	0	0	0
12. Foci of RES-cells occasionally accompanied by a few necrotic hepatocytes										
a. one or a few	18	15	27	5	12	39	28	42	12*	25*
b. several	5	8	3	0	1	6	3	5	0	3
13. Slight haematopoietic activity	2	0	0	0	1	1	0	3	0	0

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Table VI-23 - continued

Type of changes	Incidence of changes									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
14. Single cell necrosis										
a. slight	2	3	1	0	4	2	3	13**	5*	9*
b. moderate/severe	2	1	0	0	0	1	3	4	2	2
15. Focal necrosis										
a. slight	11	3*	8	2	4*	4	4	6	6	3
b. moderate	1	2	1	0	0	3	1	2	0	3
c. severe	1	0	0	2	0	3	0	1	0	1
16. Centrolobular liver-cell degeneration	1	3	3	1	0	3	2	2	0	0
17. One or a few foci of degenerated hepatocytes	1	0	7*	3	0	1	2	0	0	0
18. Haemorrhagic areas	1	0	1	0	0	0	0	1	0	0
19. Peliosis-like changes	0	1	0	2	0	1	1	0	0	0
20. Small granuloma	0	0	0	0	0	2	0	0	0	0
21. Vacuolization of hepatocytes mainly										
a. periportal										
I slight	3	6	11*	3	4	24	22	29	4*	6***
II moderate	0	2	5*	0	0	3	2	6	0	1
III severe	0	1	1	0	0	0	0	0	0	0

Table VI-23 - continued

Type of changes	Incidence of changes									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
b. diffuse										
I slight	1	0	1	0	0	0	0	0	0	0
II moderate	1	0	2	0	0	2	0	0	0	0
III severe	0	2	0	0	0	1	0	0	0	2
c. centrolobular										
I slight	0	1	0	0	0	0	0	0	0	0

---

[1] Specific hepatocellular lesions were classified according to Squire and Levitt (1975).

* P < 0.05; ** P < 0.01; *** P < 0.001, according to the Fishers' exact test (one tailed).

Adapted from Til et al. 1983.

Table VI-24 Type and Incidence of Tumors of the Mammary Glands and Incidences of Abdominal Mesotheliomas

Site and type of tumours	Incidence of tumours									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7	0
Number of animals examined	99	99	99	49	100	98	100	96	48	98
Mammary glands										
- No of tumour-bearing animals	5	8	3	0	3	41	21***	28*	21	20***
1. Adenoma										
a. single	0	0	0	0	0	6	4	2	5	2
b. two	0	0	0	0	0	1	1	1	0	0
2. Intraductal papilloma	0	0	0	0	0	0	0	0	1	0
3. Fibroadenoma										
a. single	0	1	0	0	0	25	10**	15	14	11**
b. two	0	0	0	0	0	2	3	2	2	4
c. multiple	0	0	0	0	0	3	1	1	1	3

Table VI-24 - continued

Site and type of tumours	Incidence of tumours									
	Males					Females				
	mg VCM/kg b.w./day					mg VCM/kg b.w./day				
	0	0.017	0.17	1.7	0	0	0.017	0.17	1.7*	0
4. Fibroma										
a. single	4	6	2	0	3	1	4	1	2	2
b. two	0	0	1	0	0	0	0	0	0	0
c. multiple	0	0	0	0	0	1	0	0	0	0
5. Adenocarcinoma										
a. single	0	1	0	0	0	3	0	5	1	0
b. two	1	0	0	0	0	0	0	2	0	1
Abdomen										
1. Mesothelioma	0	1	2	0	0	3	2	2	1	1

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, according to the Fishers' exact test (one tailed)

Adapted from Til et al. 1983.

VII. HUMAN HEALTH EFFECTS

A. Non-Carcinogenic Effects

Vinyl chloride can produce a number of pathological consequences in humans in addition to its carcinogenic effect. These effects can be caused by acute or chronic exposure to vinyl chloride. Unfortunately, data regarding dose-response relationships in humans are very scarce because few air measurements of vinyl chloride in the work environmental of vinyl chloride manufacturing and polymerization plants were made before 1975 (Mancuso 1975). According to OSHA (39 Federal Register 12342, April 5, 1974), several facilities revealed vinyl chloride concentrations for some job classifications as high as 229 ppm. Rowe (1975) commented that before 1960, a few jobs resulted in exposures in the range of 100 to 385 ppm, but these measurements may be high because the method of quantification measured total halogens rather than vinyl chloride alone. Nicholson et al. (1975) reported that vinyl chloride in polymerization reactors may often have exceeded 1,000 ppm and occasionally may have approached 10,000 ppm before OSHA standards were instituted. At these levels, workers experienced dizziness, headaches and/or euphoria during work periods.

Several instances of acute exposure have occurred in vinyl chloride plants. Deaths of two Canadian workers following acute exposures to vinyl chloride gas were reported by Danziger in 1960. At autopsy, there was congestion of the liver, spleen and kidneys. In another study reported by Suciu et al. (1975), exposure of workers to high concentrations of vinyl chloride produced euphoria, intoxication and narcosis. In this study, the investigators found a dose-response relationship for acute and subacute cases of "occupational disease" from air concentrations ranging from 2,298 mg/m^3 (about 900 ppm) to about 100 mg/m^3 (about 40 ppm).

In another investigation, Spirtas et al. (1975) conducted a survey of 200 vinyl chloride workers and 89 rubber plant workers (controls) in which information was sought on the frequency of eight symptoms, including dizziness, loss of consciousness, headaches, etc. The vinyl chloride workers were categoried into low and high exposure groups. Because the exposure limits had been markedly decreased a short time before the survey, the high exposure group consisted of workers who were exposed to vinyl chloride concentrations of over 200 ppm before the standard, and 20 to 30 ppm subsequently. The low exposure group consisted of workers who were exposed to 0 to 50 ppm before the standard and 0 to 10 ppm subsequent to it. Examination of the differences among the three groups indicated a statistically significant dose-response relationship for five of the eight symptoms (i.e., frequency of symptoms in the high exposure group > low exposure group > rubber workers), and a similar but non-significant trend in two of the remaining symptom categories. Thus, there appears to be a dose-response relationship between certain acute symptoms (predominantly neurological) and level of vinyl chloride exposure. The data also suggest that vinyl chloride levels below 50 ppm can produce health effects.

The earliest reports of hepatotoxicity in vinyl chloride workers were noted by Tribukh et al. (1949); however, the effects were attributed to plasticizers added in the manufacturing process. The observed concentrations of vinyl chloride ranged from 1 to 470 ppm. Since that time, impaired liver function has been noted by other investigators (Marstellar et al. 1975, Lilis et al. 1975, Popper and Thomas 1975, Jaeger 1975).

Another effect from chronic vinyl chloride exposure is a condition known as acroosteolysis, which involves bone lesions in the distal phalanges of the hands and feet and scleroderma-like skin lesions. Also associated with this condition are Raynaud's syndrome, pseudoclubbing of fingers, and numerous other symptoms. Many cases of acroosteolysis have been reported and characterized and most involve autoclave workers in vinyl chloride plants (Wilson et al. 1967, Dinman et al 1971, Harris and Adams 1967, Lilis et al. 1975).

Other long-term effects induced by vinyl chloride are disturbances of the central nervous system, pulmonary insufficiency, cardiovascular manifestations and several gastrointestinal symptoms (Miller et al. 1975, Suciu et al. 1975). These and other vinyl chloride-induced health effects are reviewed in the New York Academy of Sciences report "Toxicity of Vinyl Chloride-Polyvinyl Chloride" (Selikoff and Hammond 1975).

Reproductive effects have also been noted. According to a study by Infante (Infante 1976, Infante et al. 1976a), the incidence of birth defects for three small communities in Ohio in which vinyl chloride polymerization plants are located was significantly higher ($P<0.001$) than that in either the counties in which these communities are located or the State of Ohio. Significant excesses were observed for clubfoot and defects of the central nervous system, upper alimentary tract and genital organs. A follow-up study by Edmonds et al. (1975) identified a moderate increase in central nervous system malformations, but no association could be found with vinyl chloride exposure. In another epidemiologic study by Infante et al. (1976b), there was a significant excess fetal loss ($P<0.05$) in wives whose husbands were vinyl chloride polymerization workers compared to controls (wives of polyvinyl chloride fabrication and rubber workers). The Infante studies suggest an association between vinyl chloride and birth defects/fetal loss, but they are not yet supported by animal data. Hatch et al. (1981) examined the statistical analysis (chi-square) used in the Infante (1976a, 1976b) work and concluded that the difference in fetal loss reported as statistically significant by Infante (1976a, 1976b) was not statistically significant. Hatch et al. (1981) also concluded that the statistical test used was of rather low power, and that a negative finding with this analysis does not rule out a possible moderate effect.

Cytogenic studies have also been conducted. Picciano et al. (1977) reported no statistically significant differences in chromatid and chromosome aberrations or proportion of abnormal cells, in a group of 209 vinyl chloride exposed workers. These workers were exposed for periods ranging from 1 to 332 months to time-weighted average (TWA) levels of vinyl chloride ranging from 0.13 to 15.2 ppm. Killian et al. (1975) also reported a lack of evidence for excess chromosome breakage in a population of vinyl chloride exposed workers. In contrast, Ducatman et al. (1975) and Purchase et al. (1975) reported an increased incidence of chromosome breakage among vinyl chloride exposed workers.

Hansteen et al. (1978) and Anderson et al. (1981, 1980) showed that chromosome aberration frequencies in cultured lymphocytes from workers exposed to vinyl chloride returned to levels in the normal control range after a period without exposure to vinyl chloride or after a reduction in vinyl chloride exposure levels.

Heath et al. (1977) examined cytogenic effects in three groups of industrial workers: PVC polymerization workers (presumed high exposure), PVC processing workers (presumed low exposure) and rubber and tire manufacture workers (presumed negligible exposure). Actual vinyl chloride levels were not measured. Chromosome breakage in all three groups was significantly greater than in non-industrial controls, and overall breakage levels were similar in all three groups. The authors concluded that other agents in addition to vinyl chloride may cause cytogenic damage in workers employed in the rubber/plastics industry.

B. Carcinogenic Effects

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organ systems including angiosarcoma of the liver. Human data have been obtained primarily from occupational exposure of workers to vinyl chloride.

Epidemiologic studies of vinyl chloride exposed workers have focused on cases of angiosarcoma of the liver, a type of cancer which occurs infrequently in the general population, about 25-30 cases per year in the United States (Heath et al. 1975). Because of its rare occurrence, it is possible to infer a causal relationship between exposure to vinyl chloride and the development of this tumor. The epidemiologic evidence linking vinyl chloride to other types of cancers is more tenuous.

The first study associating vinyl chloride exposure in humans with cancer was conducted by Creech and Johnson, 1974. Three cases of angiosarcoma in workers at a polymerization plant in Louisville, Kentucky, were described. The remaining portion of this section describes some of the epidemiologic studies linking vinyl chloride with angiosarcoma and other types of cancer.

Tabershaw and Gaffey (1974) conducted a mortality study of vinyl chloride workers. Mortality calculations included only those workers who could be traced, i.e., 7,128 of 8,384 workers. These individuals were from 33 difference facilities and all had been exposed to vinyl chloride for at least one year. The mean employment duration for the group of workers under study was 80 months. Among the workers, there were 854 with exposures of 20 years or longer and 1,640 exposed 15 or more years.

The overall mortality rate among vinyl chloride workers was found to be lower, i.e., 75 percent of the expected rate compared to the general male U.S. population. The favorable overall mortality rate is a phenomenon commonly observed in working populations. Standardized mortality ratios (the ratio of the number of observed deaths in the study population to the number of deaths expected in a comparable population) for malignant neoplasms increased with increasing exposure level and/or longer duration. In the group identified as the high exposure group, there were increases in liver cancer (primarily angiosarcoma), respiratory system cancer and brain cancer. These differences were not statistically significant.

Dow Chemical Co. (Holder 1974) conducted a mortality study of 594 workers exposed to vinyl chloride in a single plant between 1942 and 1960. Workers were assigned to exposure groups based on the highest level of exposure for at least one month (low group - TWA less than 25 ppm vinyl chloride, intermediate - 25 to 200 ppm TWA, high - 200 to 300 ppm TWA). Also included in the high group were workers normally exposed to 25 to 200 ppm TWA who were also frequently exposed to excursions of 1,000 ppm. Total mortality was 91 percent of expected among the vinyl chloride exposed workers. No deaths due to liver cancer were reported, and only 13 cases of neoplasms were reported as opposed to 15.4 expected. Nine of these malignancies occurred in the high exposure group, as compared to 5.1 expected (the author stated that due to the small number of deaths, this difference was not tested for significance). Eight of these malignancies were in workers with 15 or more years of exposure.

Monson et al. (1975) conducted a proportional mortality study of workers from two vinyl chloride plants who died between 1947 and 1973. Death certificates were obtained for 142 of 161 workers (88%) who died within this time period. Deaths attributable to cancer were 50 percent higher than expected (a statistically significant difference). A 900 percent increase in cancers of the liver and biliary tract was noted (five angiosarcomas). Excluding angiosarcoma, a 275 percent excess in the number of cancers was observed. Two brain tumors (320 percent excess) and 13 lung cancers (60 percent excess) were observed. In addition, the overall cancer death rate increased during the period.

Nicholson et al. (1975) studied a group of 257 workers (of whom 255 were traced) exposed to vinyl chloride for at least five years subsequent to 1946. Their mortality status was evaluated beginning ten years after the start of employment until 1974. Exposures were estimated to often exceed 10,000 ppm. Among the 24 deaths were three cases of angiosarcoma of the liver. Preliminary findings indicated a 25 percent increase in deaths over the expected number and a 131 percent increase in all cancer deaths, although neither of these increases was statistically significant.

The National Institute for Occupational Safety and Health (NIOSH) conducted a study which involved 1,294 individuals who were exposed to vinyl chloride for at least five years, and for whom at least ten years had elapsed since initial employment. A total of 136 deaths was reported versus 126.3 expected (not a significant difference). A 49 percent increase over the expected number of cancer deaths was noted, a statistically significant factor. A statistically significant excess number of deaths occurred for brain and CNS cancer, respiratory system cancer, and biliary and liver cancer (Waxweiler et al. 1976).

Ott et al. (1975) reexamined much of the mortality data reported by Tabershaw and Gaffey (1974) and included more clearly defined exposure levels and follow-up of former company employees. The basic findings remain unchanged; no increase over expected in malignant neoplasms was found in the low exposure group (TWA from 10 to 100 ppm) and an increase in deaths due to malignant neoplasms was observed in the high exposure group (TWA of greater than 200 ppm).

Chiazze et al. (1977) reported a cross-sectional mortality study of 4,341 employees from 17 PVC plants who died between 1964 and 1973. The exposed employee population was compared with the entire U.S. population, specific for color and sex and adjusted for age. No angiosarcoma deaths were identified. Total cancer deaths increased in white employees (especially due to cancer of the digestive system). In white women employees, deaths from cancer of the breast and urinary organs were greater than expected. In a follow-up case-control analysis of breast cancer deaths among PVC fabricators, as an extension of their 1977 study, Chiazze et al. (1980) found no statistically significant relative risks for breast cancer in PVC fabricators and concluded that very large increases in risk for breast cancer did not exist among these workers.

In contrast, in a mortality study of 7,000 British workers exposed to vinyl chloride between 1940 and 1974, the investigators found no evidence of increased cancer mortality other than from liver cancer. In this study, four cases of malignant liver tumor were diagnosed, and two of these were confirmed as angiosarcoma. Both cases were in men exposed to high levels of vinyl chloride (Fox and Collier 1977).

In addition, Byren et al. (1976) traced 750 of 771 Swedish vinyl chloride plant workers. A four- to five-fold increase over expected in pancreas and liver tumors was found, and two cases were diagnosed as angiosarcoma. The numbers of other tumors did not deviate significantly from expected.

Ten cases of hepatic angiosarcoma were found among the relatively small work force employed at a vinyl chloride polymerization plant in Quebec. This is the largest number of cases to be diagnosed in a single plant (Makk et al. 1976). As a result, Delorme and Theriault (1978) retrieved more detailed information on these employees. The authors suggest that the cases of hepatic angiosarcoma appear to be associated with high vinyl chloride exposure levels and overtime work hours. No correlation was found between occurrence of this tumor and alcohol consumption or cigarette smoking.

In workers engaged in the polymerization of vinyl chloride who were studied by Popper and Thomas (1975), the characteristic hepatic fibrosis was present in all cases of angiosarcoma. Although the relation of fibrotic lesions to the development of angiosarcoma requires further study, a transition from the fibrotic stage to angiosarcoma is suggested by the focal proliferation of the sinusoidal lining cells and of the hepatocytes that are seen in the fibrotic stage, but which becomes even more pronounced in the initial stages of angiosarcoma development. These findings suggest that the fibrotic lesions without angiosarcomas, frequently observed in workers to exposed to vinyl chloride (Lilis et al. 1975), might be the prestage of developing neoplastic lesions. The diagnosis of the fibrotic lesions in these workers may imply a longer latency period for tumor initiation based on a lower exposure level. The series of changes observed in the liver appear to represent a multi-centric development of angiosarcoma and are similar to the changes induced by Thorotrast and inorganic arsenicals (Berk et al. 1976).

In the most recent update of the NIOSH register (Spirtas and Kaminski 1978) a total of 64 cases of hepatic angiosarcoma have been identified worldwide among vinyl chloride-exposed industrial workers. A listing of all documented cases by country is presented in Table VII-1. The number of cases per year is depicted in Figure VII-1. Of the 64 cases, 23 have been reported in the United States. The authors reported that both the age at diagnosis and the latency period for cancer induction appear to be increasing. They suggested three explanations for these phenomena: (1) early cases may have heavier exposures, (2) the initial cases represented more biologically susceptible individuals and (3) random fluctuation. If the trend of increased age at diagnosis and the longer latent period for hepatic angiosarcoma induction are indeed related to lower levels of occupational exposure, then the latent period for cancer induction as a result of these low levels of exposure may be longer than previously anticipated, i.e., it would be many years before the ultimate outcome of these exposures will be known.

It has been hypothesized that inhalation of low levels of vinyl chloride by the general public in the vicinity of vinyl chloride/PVC manufacturing plants could be responsible for an increased risk of developing angiosarcoma of the liver. Brady et al. (1977) examined annual rates of hepatic angiosarcoma from 1970 through 1975 in residents of the State of New York (excluding New York City). Exposures to arsenic, vinyl chloride or thorium dioxide were suggested as significant factors in the etiology of these tumors.

Table VII-1 Angiosarcoma of the Liver in Vinyl Chloride/PVC Worker

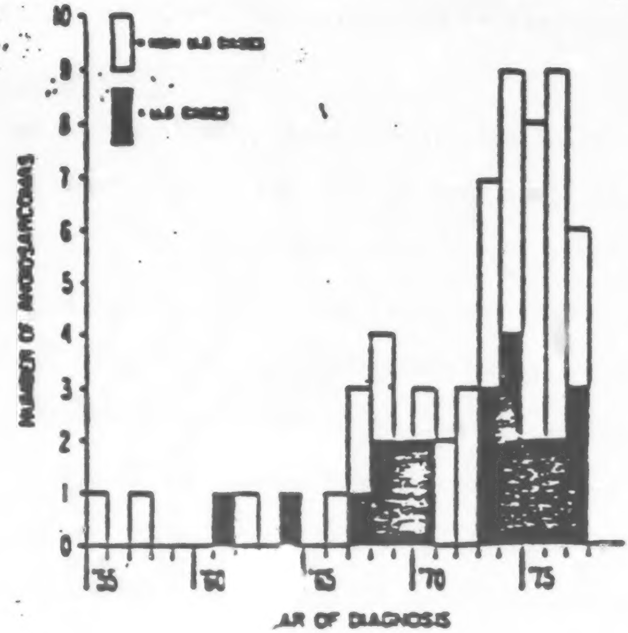
Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Belgium	01	00-00-00	00-00-00	00-00-00	00	00	00	06-29-76
Canada	01*	12-15-13	00-00-44	00-00-55	41	11	11	09-02-55
Canada	02*	03-06-14	00-00-43	00-00-57	43	14	14	12-21-55
Canada	03*	08-26-19	00-00-41	00-00-62	42	21	20	03-22-62
Canada	04*	04-05-19	00-00-45	00-00-67	48	22	22	01-21-68
Canada	05*	05-07-11	00-00-44	00-00-68	57	24	05	07-05-68
Canada	06*	12-15-19	00-00-47	00-00-71	51	24	23	04-10-71
Canada	07*	11-09-19	00-00-46	00-00-72	53	26	25	12-24-72
Canada	08	05-13-20	00-00-61	00-00-73	53	12	05	06-12-73
Canada	09	07-19-21	00-00-46	00-00-74	53	28	26	09-04-74
Canada	10	05-16-15	00-00-53	00-00-76	61	23	14	04-00-77
Czechoslovakia	01*	00-00-28	00-00-57	00-00-73	46	16	16	00-00-74
Czechoslovakia	02*	00-00-26	00-00-51	00-00-66	40	15	15	00-00-66
Fed Rep Germany	01*	06-04-30	10-01-56	09-19-68	38	12	12	01-25-69
Fed Rep Germany	02*	07-26-31	10-14-57	09-25-70	39	13	12	12-14-71
Fed Rep Germany	04	09-04-30	04-16-57	00-00-74	44	17	17	11-25-74
Fed Rep Germany	05*	01-01-32	12-16-62	00-00-75	43	13	12	01-09-75
Fed Rep Germany	07*	09-29-26	04-15-54	00-00-75	49	21	12	11-13-75
Fed Rep Germany	08*	10-19-17	04-19-54	00-00-75	58	22	21	12-25-75
Fed Rep Germany	09*	12-13-34	12-02-59	06-16-76	42	17	15	Alive
Fed Rep Germany	10*	07-25-29	10-10-55	06-28-77	47	22	22	06-28-77
Fed Rep Germany	11*	12-29-36	01-02-61	00-00-77	41	16	10	03-07-77
France	01*	04-15-24	01-00-46	02-18-67	43	21	19	02-19-67
France	02	06-03-11	07-06-59	01-08-75	63	15	12	01-24-75
France	03*	00-00-19	00-00-46	01-00-75	55	29	29	06-29-75
France	04*	01-27-27	10-19-49	01-04-76	49	26	26	01-04-76
France	05*	01-29-38	00-00-65	04-00-76	38	11	10	05-13-76
France	06*	04-14-34	00-00-58	09-00-76	42	18	17	09-12-76
France	07	00-00-27	07-01-50	07-00-76	49	26	23	07-02-76
France	08*	04-01-34	05-23-57	12-03-76	42	19	19	01-30-77
Great Britain	01*	04-20-01	00-00-44	12-00-72	71	28	22	12-00-72
Great Britain	03	06-02-37	02-00-66	12-00-74	37	09	04	12-24-74

Table VI-1 - continued

Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Italy	02*	11-13-29	00-00-57	12-13-72	43	15	06	12-00-72
Italy	03*	03-14-20	00-00-53	07-10-75	55	22	21	07-10-75
Japan	01	08-01-22	04-00-53	08-21-74	52	22	22	10-24-75
Norway	01*	12-23-15	03-00-50	12-20-71	56	22	21	01-04-72
Sweden	01*	06-23-27	08-14-51	08-00-74	43	19	18	10-20-70
Sweden	03*	06-10-10	05-00-47	03-19-76	65	29	21	03-19-76
Sweden	04*	11-16-14	00-00-46	05-12-77	62	31	31	05-12-77
U.S.A.	01*	10-17-23	12-09-48	03-03-73	49	24	21	03-03-73
U.S.A.	02*	08-19-33	11-15-55	05-00-70	37	14	13	09-28-71
U.S.A.	03*	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
U.S.A.	04*	01-15-24	07-06-52	08-19-67	43	15	15	01-07-68
U.S.A.	05*	01-25-12	06-19-44	04-09-64	52	20	20	04-09-64
U.S.A.	06*	11-23-28	01-17-62	02-00-74	46	12	12	07-24-75
U.S.A.	07*	05-03-22	08-27-44	00-00-68	45	24	17	03-23-68
U.S.A.	08*	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
U.S.A.	09*	11-08-31	05-28-45	03-01-74	43	29	24	03-00-75
U.S.A.	10*	08-16-13	06-12-51	05-00-68	55	17	17	05-10-68
U.S.A.	11*	05-27-09	10-14-46	03-00-70	61	23	23	03-16-70
U.S.A.	12*	11-17-18	09-13-49	05-02-69	50	20	19	05-02-69
U.S.A.	13*	12-01-21	12-11-42	05-00-74	52	32	26	07-04-74
U.S.A.	16*	11-04-27	05-08-50	00-00-69	41	19	04	03-27-69
U.S.A.	17*	05-06-31	06-23-55	10-11-74	43	19	19	Alive
U.S.A.	18*	04-22-28	09-15-54	00-00-75	46	21	11	11-02-75
U.S.A.	19*	00-00-15	00-00-43	06-19-75	60	32	22	04-06-76
U.S.A.	20*	08-31-17	00-00-55	01-30-76	58	21	18	01-30-77
U.S.A.	21*	09-02-09	12-00-46	00-00-77	67	30	21	01-02-77
U.S.A.	22*	10-02-23	07-11-47	01-00-76	52	29	28	12-04-76
U.S.A.	23*	00-00-23	09-00-58	04-06-73	50	15	14	04-06-73
U.S.A.	24*	05-07-17	00-00-39	05-27-77	60	38	26	05-27-77
U.S.A.	25*	08-07-10	02-00-47	03-10-77	67	30	20	03-10-77
Yugoslavia	01*	04-05-14	00-00-53	04-08-73	59	20	20	04-08-73
Yugoslavia	02*	11-15-31	00-00-50	07-12-73	42	23	18	07-12-73
Total Reported Cases	64							

Adapted from Spirtas and Kaminski 1978.

Figure VII-1 Number of Cases of Vinyl Chloride/PVC Related Angiosarcomas Reported to NIOSH by Year of Diagnosis (Representing only 63 of the 64 Cases Known to NIOSH Since Information on Diagnosis is Missing for One Case



Adapted from Spirtas and Kaminski 1978.

Direct exposure to these agents could not be demonstrated in 19 of the 26 study cases. Five of the 19 patients lived closer to vinyl chloride plants than did their matched controls. This may lend some support to the idea that "indirect modes of exposure, not specifically related to occupation, might be important in the etiology of this disorder" (Brady et al. 1971).

Falk et al. (1981) described a nationwide survey of hepatic angiosarcoma in the United States from 1964 to 1974 which identified 168 cases. Of these, 42 cases were associated with known etiologic factors including exposure to vinyl chloride, use of thorotrast, exposure to inorganic arsenic and treatment with androgenic-anabolic steriods. The remaining cases were of uncertain etiology. The authors concluded that hepatic angiosarcoma most often affects males, peaks in the sixth and seventh decades of life, and appears to occur more often in industrial areas of the Northeast and Midwest. These authors also noted a high relative risk for PVC polymerization workers.

IARC (1979) examined the available data on humans and concluded that exposure to vinyl chloride results in an increased carcinogenic risk to humans. The organ systems most likely to be affected were the liver, brain, lung and hemato- and lymphopoietic systems.

VIII. MECHANISMS OF TOXICITY

The mechanisms by which vinyl chloride causes non-carcinogenic injury are unknown. It is theorized that the toxicity of this compound is attributable to its enzymatic oxidation to reactive polar metabolites, possible chloroethylene oxide or chloroacetaldehyde (see Pharmacokinetics section).

Ward et al. (1976) hypothesized that an immunological mechanism is responsible for the non-carcinogenic pathological effects of vinyl chloride exposure. According to this model, a metabolite of vinyl chloride binds to plasma protein, producing an antibody response. The antigen and resulting immunoglobulin interact to produce a soluble complex which causes vascular occlusion, platelet aggregation and other adverse effects which explain the observed symptoms of the disease. An investigation of workers with "vinyl chloride disease" showed the presence of circulating immune complexes in 19 of 28 patients. Abnormalities were also detected in some workers exposed to vinyl chloride who had few or no overt clinical signs.

Over the past several decades, scientists have undertaken considerable research in an effort to establish the mechanism(s) by which chemical substances cause their carcinogenic effects. The somatic cell mutation theory of carcinogenicity suggests that for a carcinogenic response to occur, an irreversible change must occur in the cell which results in proliferation of a neoplasm. This change reflects a mutational event in the DNA of that cell, suggesting that the chemical carcinogen must interact directly with or otherwise alter the DNA to initiate the change. In recent years, however, some substances have been shown to be carcinogenic, but by mechanisms with no apparent direct interaction with or alteration of the DNA of the cell by the substance. Presumably, these compounds are not capable of initiating the alteration of a normal cell to a neoplastic one, but can facilitate expression of neoplastic response in latent cells. Carcinogens now are often classified into two broad categories: genotoxic and epigenetic or nongenotoxic.

The mechanism by which a compound causes its carcinogenic effect can rarely be determined by the chronic testing of whole animals, as in the NTP bioassay. Thus, a large number of short-term *in vitro* and *in vivo* assay systems have been developed for the purpose of elucidating mechanisms. Since most of the *in vitro* testing systems measure mutational events, and many carcinogens are mutagens, it is suggested that positive results in certain of these test systems indicate genotoxicity. The decision as to whether a substance is genotoxic may be made qualitatively on the basis of several criteria: (1) a reliable, positive demonstration of genotoxicity in appropriate prokaryotic and eukaryotic systems *in vitro*, (2) studies on binding to DNA and (3) evidence of biochemical or biologic consequences of DNA damage (Weisburger and Williams 1981).

No single test system appears capable of identifying all carcinogens that are genotoxic. Therefore, a number of scientists have proposed testing batteries such that the results from each test within the battery, when evaluated in conjunction with the others, will enable researchers to determine the mechanism of carcinogenicity of a particular compound. Vinyl chloride has not been systematically studied in any specific battery of tests, but has been evaluated in a number of test systems that have been proposed for inclusion in one or more batteries. Table VIII-1 summarizes some of the mutagenicity studies on vinyl chloride which have demonstrated the chemical's genotoxic potential. The studies have been divided according to the three criteria for genotoxicity (Weisburger and Williams 1981) outlined above.

Considering all of the data on vinyl chloride, it is probable that vinyl chloride exerts its carcinogenicity through genotoxic mechanisms.

Table VIII-1 Results of Vinyl Chloride Mutagenicity Studies

A. Assay system	Results	References
In Vitro prokaryotic and eukaryotic systems		
Metabolically activated *Salmonella typhimurium* system (Ames)	+	Bartsch et al., 1975 McCann et al., 1975 Elmore et al, 1976 Rannug et al, 1974 Garro et al, 1976
Escherichia coli K12 bioauxotrophic strain	+	Greim et al., 1975
Yeast		Loprieno et al, 1976, 1977
Germ cells of *Drosophilia*	+	Verburgt and Vogel, 1977
Chinese hamster V79 cells	+	Huberman et al., 1975
B. DNA Binding Studies		
Mouse tissues (brain, lung, liver, kidney, spleen, pancreas and testes) *in vitro*	+ (Irreversible binding to RNA and DNA)	Bergman, 1982
Rat liver microsomes, reconstituted cytochrome P-450 systems and isolated hepatocytes	+ (Irreversible binding to protein and DNA)	Guengerich et al., 1981
Rat liver microsomes with NADPH	+ (Alkylation of RNA)	Laib and Bolt, 1977
C. Biochemical or biologic consequences of DNA damage		
Bone marrow cells of rats (*in vivo*)	+ (Chromosome damage)	Anderson and Richardson, 1976
Bone marrow cells of Chinese hamsters (*in vivo*)	+ (Chromosome aberrations and sister-chromatid-exchanges)	Basler and Rohrborn, 1980
Cultured peripheral lymphocytes in humans (vinyl chloride exposed workers)	+ (Chromosomal abnormalities)	Purchase et al., 1978 Purchase et al., 1975 Ducatman et al., 1975

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IX. QUANTIFICATION OF TOXICOLOGICAL EFFECTS FOR VINYL CHLORIDE

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{AADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70 \text{ kg})}{(\text{Uncertainty factor})(2 \text{ liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" which is the highest reported long-term dose observed not to produce any adverse effect, or a "minimal-effect-level" which is the lowest studied concentration at which adverse health effects were observed is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for those numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive than animals to the toxic effects of chemicals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population; differing sensitivity of individuals to toxins.

The guidelines set forth by the NAS (1977) are used in establishing uncertainty factors. These guidelines are: an uncertainty factor of 10 is

Current understanding of the biological mechanisms involved in cancer does not indicate a clear choice among the models. The estimates of incremental risks associated with exposure to low doses of potential carcinogens can differ by several orders of magnitude when these models are applied. The multistage model does not necessarily give the highest or lowest risk estimates at low doses. Whether it is the most conservative, least conservative or predicts a risk in the middle of the range of risks predicted by other models is chemical specific.

The scientific data base, which is used to support the estimating of risk rate levels as well as other scientific endeavors, has an inherent uncertainty. In addition, in many areas, only limited knowledge exists concerning the health effects of contaminants at levels found in drinking water. Thus, the dose-response data gathered at high levels of exposure are used for extrapolation to estimate responses at levels of exposure nearer to the range in which a standard might be set. In most cases, data are available only for animals; thus, there is uncertainty when the data are extrapolated to humans. When estimating risk rate levels, there are several other areas of uncertainty such as the effect of age, sex, species and target organ of the test animals used in the experiment, as well as the exposure mode and dosing rates. Additional uncertainty exists when there is exposure to more than one contaminant, due to the lack of information about possible additive, synergistic or antagonistic interactions.

used if there are valid experimental results from studies on prolonged ingestion by man, with no evidence of carcinogenicity; an uncertainty factor of 100 is used if there exist valid results of long-term feeding studies on experimental animals or, in the absence of human studies, valid animal studies on one or more species, with no indication of carcinogenicity; and an uncertainty factor of 1000 is used if there are no long-term or acute human data, scanty results on experimental animals and no evidence of carcinogenicity.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's CAG has used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. In order to predict the risk for humans from animal data, the data must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used.

Excess cancer risk rates can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model.

A. Non-Carcinogenic Effects

Vinyl chloride has been shown to cause non-carcinogenic effects in animals and humans. Acute and chronic toxicity studies have shown the major effects to be congestion and edema of the lungs and hyperemia of the kidneys and liver. Other non-carcinogenic effects have been noted, including disturbances of the central nervous system, pulmonary insufficiency, cardiovascular manifestations, gastrointestinal symptoms and acroosteolysis.

Acute toxicity tests with vinyl chloride were carried out by Patty et al. (1930). Single exposures of guinea pigs to vinyl chloride gas, 10 percent in air (100,000 ppm), resulted in narcosis and death within 30 to 60 minutes. Inhalation of lower concentrations resulted in ataxia and narcosis. Pathological findings at necropsy were congestion and edema of the lungs and hyperemia of the kidneys and liver. Mastrometto et al. (1960) exposed mice, rats and guinea pigs in an inhalation chamber to 10, 20 or 30 per cent vinyl chloride in air for 1 to 30 minutes. The principal pathological changes observed were pulmonary edema and hemorrhages, and congestion of the liver and kidneys.

In a chronic inhalation exposure study (Torkelsen et al. 1961), rats, rabbits, guinea pigs and dogs were exposed repeatedly for up to six months to 50, 100, 200 or 500 ppm vinyl chloride in air. Detectable changes occurred at all but the lowest concentration. Rats exposed to 100 ppm (7 hours/day for 6 months) were judged normal on the basis of appearance, mortality, growth, hematological examination and other factors. Slight increases were found in the average weights of the livers of male and female rats. Rats, guinea pigs, rabbits and dogs exposed to 50 ppm (7 hours/day for 6 months) appeared to be normal in appearance, mortality and growth, and the increase in weight of the rat livers did not occur at this concentration. At higher doses, pathological changes were increasingly more pronounced. Basalaev et al. (1972) administered gaseous vinyl chloride to rats and rabbits at a concentration of 0.03 to 0.04 mg/L for 4 hours/day for 6 months. Cardiovascular disorders, changes in the bioelectric activity of the hypothalamus, hyperadrenalinemia, osteoporosis and resorption of bone tissue were observed.

Feron et al. (1981) carried out a lifespan oral toxicity study of vinyl chloride in rats. VCM was incorporated into the diet, or gastric intubation of a 10% VCM solution in soybean oil was used. Groups of 60 to 80 male and 60 to 80 female Wistar rats were exposed to 0, 1.7, 5.0 and 14.1 mg/kg bw vinyl chloride in the diet, or 300 mg/kg bw by gastric intubation. A variety of carcinogenic and noncarcinogenic effects were observed at all dose levels. At the 14.1 and 300 mg/kg doses, shortened blood-clotting times, slightly increased α-foetoprotein levels in the blood serum, liver enlargement and an increased hematopoietic activity in the spleen were observed. Non-neoplastic liver lesions consisting of pronounced swelling, discoloration and altered consistency of the lobes as well as nodules and nodule-like processes were observed. At the lower dose levels of 1.7 and 5.0 mg/kg bw, histopathological changes in the liver were observed including clear-cell foci, extensive necrosis, cysts, and liver-cell polymorphism.

Suciu et al. (1975) examined exposure of workers to vinyl chloride at high concentrations. Air concentrations ranging from 100 mg/m^3 (40 ppm) to 2,298 mg/m3 (900 ppm) produced euphoria, intoxication and narcosis, in a dose-response relationship. In an epidemiological investigation, Spirtas et al. (1975) conducted a survey of 200 vinyl chloride workers and 89 rubber plant workers (controls). The vinyl chloride workers were categorized into low and high exposure groups. The high exposure group consisted of workers who were exposed to concentrations ranging from 20 to 200 ppm and the low exposure group consisted of workers exposed to 0 to 50 ppm vinyl chloride. Information was sought on the frequency of eight symptoms, including dizziness, nausea, headache and weakness. The results showed a statistically significant dose-response relationship for 5 of the 8 symptoms when comparing vinyl chloride workers with rubber workers, and between high and low exposure vinyl chloride workers. A similar but non-significant trend in the remaining symptom categories was also noted.

B. Quantification of Non-Carcinogenic Effects

There is concluded to be insufficient data for calculation of one-day health advisories (HAs). The subchronic toxicity study with oral exposure of rats to VCM for six months by Feron et al. (1975) was selected as the basis for ten-day HAs. The Feron et al (1975) study is adequate for calculations of ten-day HAs, and it is the only available subchronic study with oral exposure. The ten-day HAs are also proposed as conservative estimates for one-day HAs.

The 10-day HAs, as well as the 1-day HAs, for an adult and a child are calculated as follows:

Ten-Day Health Advisory for an Adult

$$\frac{(30\ \text{mg/kg})\ (6/7)\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 9.0\ \text{mg/L}$$

Ten-Day Health Advisory For a Child

$$\frac{(30\ \text{mg/kg})\ (6/7)\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})}\ 2.6\ \text{mg/L}$$

where:

30 mg/kg = NOEL for subchronic toxicity from the Feron et al. (1975) study

6/7 = expansion of 6 days/week treatment in the Feron et al. (1975) study to 7 days/week to represent daily exposure

70 kg = assumed adult weight

10 kg = assumed child weight

2 L = assumed amount of water consumed by an adult

1 L = assumed amount of water consumed by a child

100 = uncertainty factor for extrapolating an animal study to humans and for protection of the most sensitive members of the population

In the calculation of an adjusted ADI (AADI), a chronic study in which animals or humans are exposed to the chemical at various dose levels with a no-observed-effect-level or a minimal-effect-level being identified is used. Ideally, the study should use the oral route of exposure. For vinyl chloride, the toxicological studies which fit some of the above criteria are the Feron et al. (1981) and Torkelson et al. (1961) studies. The Torkelson et al. (1961) study examined vinyl chloride inhalation exposure in rats, rabbits, guinea pigs and dogs at various dose levels. At 100 ppm, the only adverse effect noted was the slight increase in the weight of the liver in the rat, but not in the other species. No adverse effects were found at 50 ppm.

Thus, a no-effect-level of 50 ppm could be used for the derivation of the AADI. A major limitation of this study is that exposure was by inhalation and, therefore, a conversion factor would be required to convert from inhalation to ingestion exposure.

The Feron et al. (1981) study is not proposed for use in an AADI calculation because carcinogenic as well as noncarcinogenic effects were observed at all dose levels. Til et al. (1983), in a final report that is unpublished, have extended the earlier work by Feron et al. (1981) to include lower doses with basically the protocol used in the latter study. There was a significant ($P<0.05$, Fisher's Exact Test) increase in the incidence of basophilic foci, a sign of cellular alteration, in the liver in all treated groups of female rats. Basophilic foci in the liver were found as follows: 9/98 in one matched control group, 4/99 in another matched control group, 21/100 in the lower-dose group, 26/96 in the mid-dose group and 21/99 in the high-dose group. Hepatocellular carcinoma and/or angiosarcoma in the liver and neoplastic nodules in the liver were observed in mid- and high-dose female rats, and neoplastic nodule formation was detected in the liver of one low-dose female rat. Hepatocellular carcinoma was observed in one matched control female rat. Frank carcinogenicity and other non-neoplastic liver effects were not apparent in the low-dose and mid-dose groups, and the mid-dose (0.13 mg/kg/day) was selected for calculation of an AADI based on noncarcinogenic effects. The investigators concluded that the doses of 0.014 and 0.13 mg/kg/day (low- and mid-doses) may increase the incidence of basophilic foci of cellular alteration in liver of female rats. However, basophilic foci by themselves are concluded not to represent an adverse effect on the liver in the absence of additional effects indicative of liver lesions as were found in the 1.7 mg/kg/day group, and a dose-related increase in basophilic foci is not evident. Therefore, the dose of 0.13 mg/kg/day is taken as a no-observed-adverse-effect-level (NOAEL) for the AADI calculation.

Using the 0.13 mg/kg/day NOAEL from the Til et al. (1983) study, the AADI calculation is as follows:

$$\frac{(0.13\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.046\ \text{mg /L}$$

where:

0.13 mg/kg/day = NOAEL from the Til et al. (1983) study

70 kg = assumed weight of an adult

2 L = water consumption per day for an adult human

100 = uncertainty factor in a chronic animal study where a no-observed-adverse-effect-level was not apparent

Thus, the AADI for vinyl chloride using noncarcinogenic data and 100 percent exposure from drinking water would be 0.046 mg/L. This number may be appropriately reduced if there is shown to be significant vinyl chloride exposure from other sources, such as food and air.

C. Carcinogenic Effects

Vinyl chloride has been shown to have carcinogenic effects in animals and humans. Viola et al. (1971) reported the carcinogenic response of male rats (AR/IRE Wistar strain) exposed to vinyl chloride by inhalation. Rats exposed to 30,000 ppm vinyl chloride for 4 hours/ day, 5 days/week for 12 months, demonstrated an increased incidence of skin carcinomas, lung adenocarcinomas and bone osteochondromas over controls.

Caputo et al. (1974) exposed male and female rats (A and IRE Wistar strain) by inhalation to 0, 50, 500, 2,000, 5,000, 10,000 and 20,000 ppm vinyl chloride. Liver angiosarcomas, lung adenocarcinomas and skin squamous cell carcinomas were observed in all groups except those exposed to 50 ppm. Tumors appeared between 8 and 13 months from the beginning of the inhalation treatment.

Maltoni (1981) conducted a series of inhalation and ingestion studies examining the carcinogenic effects of vinyl chloride. Vinyl chloride caused tumors in all the animal systems tested (mice, rats and hamsters), both through inhalation and ingestion exposure. In one study, Sprague-Dawley rats were exposed by inhalation to vinyl chloride at concentrations ranging from 50 to 100,000 ppm for 52 weeks. Angiosarcomas of liver, zymbal gland carcinomas, skin carcinomas, mammary carcinomas and other tumors were observed. One ingestion study showed the occurrence of angiosarcomas of the liver, mammary carcinomas and other tumors at 50.0 mg/kg.

As discussed in the "Non-Carcinogenic Effects" section, Feron et al. (1981) carried out a lifespan oral toxicity study of vinyl chloride in rats. Wistar rats were exposed to 0, 1.7, 5.0 and 14.1 mg/kg bw vinyl chloride in the diet, or 300 mg/kg bw vinyl chloride by gastric intubation. The results showed that rats exposed to VCM at levels of 5.0 mg/kg bw or more demonstrated hepatic angiosarcomas, pulmonary angiosarcomas, and at the higher levels, a few extra-hepatic abdominal angiosarcomas. At the lowest exposure level of 1.7 mg/kg vinyl chloride, liver-cell tumors and an increased incidence of foci of cellular alteration were noted. The author concluded that vinyl chloride is a carcinogen when administered by the oral route, and that the tumor response seems to shift from the exclusive development of angiosarcomas at very high levels to the exclusive induction of hepatocellular tumors at low levels of exposure.

Epidemiological studies have also been conducted to examine the carcinogenic effects of vinyl chloride. The first report associating vinyl chloride exposure of humans with cancer (Creech and Johnson 1974) described three cases of angiosarcoma of the liver in workers at a polymerization plant in Louisville, Kentucky. Since that time, a number of studies have also demonstrated this association.

Monson et al. (1975) conducted a proportional mortality study of workers from two vinyl chloride plants who died between 1947 and 1973. Death certificates were obtained for 142 of 161 workers (88%) who died within this time period. Deaths attributable to cancer were 50 percent higher than expected (a statistically significant difference). A 900 percent increase in cancers of the liver and biliary tract was noted (five angiosarcomas). Excluding angiosarcoma, a 275 percent excess in numbers of cancers was observed. Nicholson et al. (1975) studied a group of 257 workers (of whom 255 were traced) exposed to vinyl chloride for at least 5 years in a polymerization facility. Exposures were estimated to often exceed 10,000 ppm. Their mortality status was evaluated beginning 10 years after start of employment until 1974. Among the 24 deaths were 3 cases of angiosarcoma of the liver. Preliminary findings indicated a 25 percent increase in deaths over the expected number and a 131 percent increase in all cancer deaths, although neither of these increases was statistically significant.

NIOSH conducted a study which involved 1,294 individuals who were exposed to vinyl chloride for at least 5 years, and for whom at least 10 years had elapsed since initial employment. A total of 136 deaths was reported versus 126.3 expected (not a significant difference). A 49 percent increase over the expected number of cancer deaths was noted, a statistically significant factor. A statistically significant excess number of deaths occurred for brain and CNS cancer, respiratory cancer, and biliary and liver cancer (Waxweiler et al. 1976).

According to IARC (1979), vinyl chloride is a human and animal carcinogen. IARC's evaluation of the chemical is as follows: "Vinyl chloride was tested in rats by oral, subcutaneous and intraperitoneal administration and in mice, rats and hamsters by inhalation exposure. Following oral and inhalation exposure, vinyl chloride was carcinogenic in all three species, producing tumors at different sites, including angiosarcoma of the liver. Vinyl chloride was carcinogenic in rats following prenatal exposure. A dose-response has been demonstrated.

Vinyl chloride is a human carcinogen. Its target organs are the liver, brain, lung and haemo-lymphopoietic system. Similar carcinogenic effects were first demonstrated in rats and were later confirmed in mice and hamsters. Although evidence of a carcinogenic effect of vinyl chloride in humans has come from groups occupationally exposed to high doses of vinyl chloride, there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans."

D. Quantification of Carcinogenic Effects

Many studies were considered for use in performing the carcinogenicity risk assessment to quantify the carcinogenic effects of vinyl chloride. In particular, human data exist for vinyl chloride and it would be advantageous to use such data in the risk assessment procedure. The human studies available, however, do not provide dose-response data that is needed for the calculation of the risk values, and thus, human data were not used for the risk assessment.

EPA's CAG and NAS used the linear multistage model to calculate the projected excess cancer risk resulting from lifetime exposure to vinyl chloride through the drinking water. The CAG numbers were calculated assuming consumption of 2 liters of drinking water and 6.5 grams fish and shellfish per day, and were published in the Ambient Water Quality Criteria Document for Vinyl Chloride, USEPA 440/5-80-078. For vinyl chloride, CAG used the incidence of total tumors in rats exposed through inhalation (Maltoni et al. 1975) to calculate the excess cancer risk. They calculated that consuming 2 liters of water per day having a vinyl chloride concentration of 200 μg/L, 20 μg/L or 2 μg/L would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}) or 1,000,000 (10^{-6}) respectively, per lifetime.

There are several problems with the data used by CAG in risk estimation. The major problem is that inhalation data were used, and the relationship between oral and inhalation exposure toxicity is not well understood.

NAS used ingestion data from the Maltoni et al. (1975) study in their calculation of excess carcinogenic risk numbers. In this study, rats were given vinyl chloride in olive oil by gavage, four or five times per week for 52 weeks and held for their life span. This experiment was not completed at the time NAS performed its computations, but the available data did indicate the development of liver angiosarcomas and other tumors in rats exposed to 16.65 mg/kg. NAS made the decision to use this study because it was thought that the limited gavage data were still superior to completed inhalation studies for assessing risk by the oral route.

NAS calculated that consuming 2 liters of water per day over a lifetime at a vinyl chloride concentration of 100 μg/L, 10 μg/L or 1 μg/L would increase the risk of one excess cancer per 10,000 (10^{-4})), 100,000 (10^{-5}), or 1,000,000 (10^{-6}) people exposed, respectively (NAS 1977).

The major problem with the NAS data is that the Maltoni experiment was not completed at the time the risk estimates were calculated, and thus, the data cannot be considered definitive. Since that time, however, the Maltoni experiment has been completed, and the NAS (1983) reexamined the data and decided to continue using the 1977 risk estimates. Using the NAS (1983) estimate, the excess cancer risk concentrations associated with 10^{-4}, 10^{-5} and 10^{-6} excess risk rates are 100 µg/L, 10 µg/L and 1 µg/L, respectively.

Neither a World Health Organization action level nor, previously, an EPA Health Advisory number have been calculated for vinyl chloride.

Interactions of vinyl chloride with other chemicals have also been demonstrated. Ingestion of ethanol was shown to increase the incidence of liver tumors in rats (Radike et al. 1977) and vinyl chloride was demonstrated to have protective effects when administered with 1,1-dichloroethylene (Jaeger 1975).

In the quantification of toxicological effects for a chemical, consideration should be given to subgroups within the general population which are at greater than average risk upon exposure to the chemical. Animal studies have indicated that older individuals, females, newborns and alcohol consumers may be particularly sensitive to the effects of vinyl chloride.

EPA's CAG has recently recalculated its excess carcinogenic risk estimates resulting from lifetime exposure to vinyl chloride through the drinking water. CAG based its preliminary revised risk estimates (1984) on the Feron et al. (1981) study. The total number of tumors, considering tumors of the lung and liver, in rats exposed through the diet was used to calculate the excess cancer risk. They calculated that consuming 2 liters of water per day having a vinyl chloride concentration of 1.5 μg/L, 0.15 μg/L and 0.015 μg/L would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}) or 1,000,000 (10^{-6}) people exposed, respectively, per lifetime. The quantitative risk assessment prepared by the CAG is in Appendix 1. The CAG is presently reassessing the cancer risk estimate based on the Feron et al. (1981) study by taking into account the more recent data by Til et al. (1983) which essentially is an extension of the earlier Feron et al. (1981) work to include lower doses.

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APPENDIX 1

UNIT RISK ASSESSMENT FOR VINYL CHLORIDE

The data used to estimate a unit risk for oral exposure to vinyl chloride are based on the Feron et al. (1981) study. The statistically significant increases reported for liver and lung tumors were considered biologically significant. For the liver tumors, neoplastic nodules were considered a progression toward hepatocellular carcinomas, and these are included in the analysis in Tables 1 and 2. Extrapolations using the linearized multistage model show values of q_1^* for the individual tumors ranging from 8.8×10^{-2} to 1.3×10^{-1} for the males and from 5.8×10^{-2} to 1.3 for the females. The value of q_1^* based on males was 3.0×10^{-1} for liver tumors and 2.9×10^{-1} based on all tumors combined. For the females the value of q_1^* based on liver tumors was 1.9 and for all tumors combined was 2.3. All units of q_1^* are per mg/kg/day.

Before proceeding with the unit risk estimates an explanation of the total tumor counts in Tables 1 and 2 is necessary. For the liver all animals with hepatocellular carcinomas were assumed to also have the neoplastic nodules. Thus, only the neoplastic nodules and liver angiosarcomas were added to derive the total liver tumors. Otherwise, the totals would have exceeded the number of animals examined. Also, in adding the lung and liver tumors, the totals were not allowed to exceed one less than the number examined. The

Table 1 Type and Incidence of Statistically Significant Treatment-Releated Changes in the Liver and Lung of Male Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included

	Treatment group (mg/kg/day)				q_1^{*}[a]	95% lower-limit concentration associated with risk (ug/L)[b]		
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	55	58	56	59				
Liver								
Neoplastic nodules	0	1	7	23	2.1×10^{-1}	16.7	1.7	0.2
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}	39.8	4.0	0.4
Angiosarcomas	0	0	6	27	1.3×10^{-1}	27.0	2.7	0.3
Total liver tumors[d]	0	2	13	50	3.0×10^{-1}	11.7	1.2	0.1
Lung								
Angiosarcomas	0	0	4	19	1.1×10^{-1}	31.8	3.2	0.3
Total animal with tumors[e]	0	2	17	58	2.9×10^{-1}	12.1	1.2	0.1

[a] Human equivalent $q_1^* = q_1^*$ (a) $(W_h/W_a)^{1/3}$ in $(mg/kg/day)^{-1}$.

[b] Concentration in ug/L = $(-35{,}000/q_1^*)$ ln(1-R).

[c] Found dead or killed in extremis or terminally.

[d] Sum of neoplastic nodules and liver angiosarcomas.

[e] Total must be at least less than total examined.

Table 2 Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Female Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included

	Treatment group (mg/kg/day)				q_1^{*a}	95% lower-limit concentration associated with risk (ug/L)[b]		
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	57	58	59	57				
Liver								
Neoplastic nodules	2	26	39	44	1.3	2.7	0.3	0.03
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}	70.0	0.7	0.07
Angiosarcomas	0	0	2	9	8.8×10^{-2}	39.8	4.0	0.4
Total liver tumors[d]	2	26	41	53	1.9	1.8	0.2	0.02
Lung								
Angiosarcomas	0	0	1	5	5.8×10^{-2}	60.3	6.0	0.6
Total animal with tumors[e]	2	26	42	56	2.3	1.5	0.2	0.02

[a] Human equivalent $q_1^* = q_1^* (a) (W_h/W_a)^{1/3}$ in $(mg/kg/day)^{-1}$.

[b] Concentration in $\mu g/L = (-35,000/q_1^*) \ln(1-R)$.

[c] Found dead or killed in extremis or terminally.

[d] Sum of neoplastic nodules and liver angiosarcomas.

[e] Total must be at least less than total examined.

result of this latter restriction was to raise the value of q_1^* slightly due to increased variance. In fitting the response data in Tables 1 and 2 with the human equivalent dosages, the human equivalent dosages were derived by dividing the corresponding animal dosages by $(W_h/W_a)^{1/3}$. The human weight (W_h) was assumed to be 70 kg; the male rats were estimated to weight 350 g and the female rats were estimated to weigh 200 g (Figure 1). Thus, the corresponding human equivalent dosages were 0, 0.29, 0.85, and 2.41 mg/kg/day based on the male rats, and 0, 0.24, 0.71 and 2 mg/kg/day based on the female rats.

When the response and human equivalent dose data were fit to the linearized multistage model, the 95% upper limit on the largest linear term (Table 2) was:

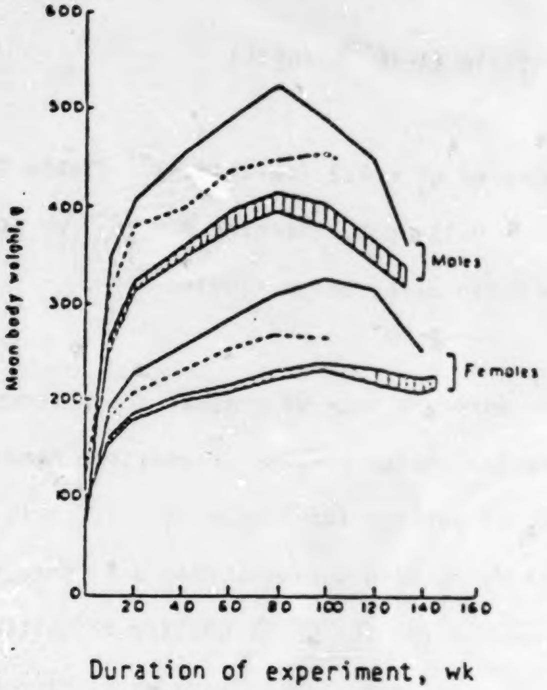
$$q_1^* = 2.3 \text{ (mg/kg/day)}^{-1}$$

To derive an estimate of the 95% lower level of concentration, d, corresponding to a 95% upper level of risk, R, the following equation is used:

$$R = 1-e^{-q_1^*d}$$

where d is the lower limit on dose in mg/kg/day. To solve for d in ug/L, we use the transformation

$$1 \text{ mg/kg/day} \times (70 \text{ kg}/2 \text{ L}) \times 1{,}000 \text{ ug/mg} = 35{,}000 \text{ ug/L}$$



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[a] The weight curves of the rats receiving 0, 1.7, 5.0 or 14.1 mg VCM/kg body weight/day from the 10% PVC diets fed for four hours each day all lie within the shaded area.

Adapted from Feron et al. 1981.

Figure 1 Average Body Weights of the Extra Controls Fed the 10%-PVC Diet Ad Libitum (-) and of the Rats Given 300 mg VCM/kg Body Weight in Oil by Gavage[a]

If we set $R = 10^{-5}$ then

$$d = (-35{,}000/q_1^*) \ln (1-10^{-5}) \text{ (ug/L)}.$$

For the highest value of $q_1^* = 2.3$ (mg/kg/day)$^{-1}$ (Table 2), setting $R = 10^{-5}$ yields a value of $d = 0.15$ ug/L. Setting $R = 10^{-4}$ or 10^{-6} yields values of $d = 1.5$ ug/L and $d = 0.015$ ug/L, respectively.

For comparison purposes only we compare the potency of vinyl chloride by the diet versus the inhalation routes. A previous memo we sent you estimated the 95% upper limit of potency for VCM as $q_1^* = 1.7 \times 10^{-2}$ (mg/kg/day)$^{-1}$ based on an inhalation study showing angiosarcomas and other tumors in rats. That potency estimate was derived for water quality criterion purposes. In that document an inhalation to ingestion by gavage relationship of 1 ppm inhaled = 2.28 mg/kg/day ingested was derived for 200 g rats based on VCM uptake study. Without that adjustment for route differences, a direct transformation based on a 70 kg human breathing 20 m^3/day would have yielded a 1 ppm inhaled = 0.76 mg/kg/day relationship and a $q_1^* = 5.2 \times 10^{-2}$ mg/kg/day, still 44 times less than the estimate from the diet study.

In summary, the VCM potency estimates are reported in Table 3.

Table 3 VCM Potency Estimates

Route	Potency	95% lower limit concentration associated with risk (ug/L)		
	$q_1^*(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Oral				
Based on diet study	2.3	1.5	0.15	0.015
Based on inhalation study	1.7×10^{-2}	200	20.0	2.0
Inhalation				
Based on inhalation study	5.2×10^{-2}	67.3	6.7	0.7